TITLE OF THE INVENTION

BIARYL SUBSTITUTED PYRAZINONES AS SODIUM CHANNEL BLOCKERS

FIELD OF THE INVENTION

The present invention is directed to a series of biaryl substituted pyrazinone compounds. In particular, this invention is directed to biaryl substituted pyrazinones that are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including disorders of bladder function, pruritis, itchiness, allergic dermatitis and disorders of the central nervous system (CNS) such as epilepsy, manic depression, bipolar disorder, depression, anxiety and diabetic neuropathy.

BACKGROUND OF THE INVENTION

Voltage-gated ion channels allow electrically excitable cells to generate and propagate action potentials and therefore are crucial for nerve and muscle function. Sodium channels play a special role by mediating rapid depolarization, which constitutes the rising phase of the action potential and in turn activates voltage-gated calcium and potassium channels. Voltage-gated sodium channels represent a multigene family. Nine sodium channel subtypes have been cloned and functionally expressed to date. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug Discovery Today* **5**, 506-520 (2000)]. They are differentially expressed throughout muscle and nerve tissues and show distinct biophysical properties. All voltage-gated sodium channels are characterized by a high degree of selectivity for sodium over other ions and by their voltage-dependent gating. [Catterall, W. A. Structure and function of voltage-gated sodium and calcium channels. *Current Opinion in Neurobiology* **1**, 5-13 (1991)]. At negative or hyperpolarized membrane potentials, sodium channels are closed. Following membrane depolarization, sodium channels open rapidly and then inactivate. Sodium channels only conduct currents in the open state and, once inactivated, have to return to the resting state, favored by membrane hyperpolarization, before they can reopen. Different sodium channel subtypes vary in the voltage range over which they activate and inactivate as well as in their activation and inactivation kinetics.

Sodium channels are the target of a diverse array of pharmacological agents, including neurotoxins, antiarrhythmics, anticonvulsants and local anesthetics. [Clare, J. J., Tate, S. N., Nobbs, M. & Romanos, M. A. Voltage-gated sodium channels as therapeutic targets. *Drug Discovery Today* **5**, 506-520 (2000)]. Several regions in the sodium channel secondary structure are involved in interactions with these blockers and most are highly conserved. Indeed, most sodium channel blockers known to date interact with similar potency with all channel subtypes. Nevertheless, it has been possible to produce

sodium channel blockers with therapeutic selectivity and a sufficient therapeutic window for the treatment of epilepsy (e.g. lamotrigine, phenytoin and carbamazepine) and certain cardiac arrhythmias (e.g. lignocaine, tocainide and mexiletine).

It is well known that the voltage-gated Na^+ channels in nerves play a critical role in neuropathic pain. Injuries of the peripheral nervous system often result in neuropathic pain persisting long after the initial injury resolves. Examples of neuropathic pain include, but are not limited to, postherpetic neuralgia, trigeminal neuralgia, diabetic neuropathy, chronic lower back pain, phantom limb pain, pain resulting from cancer and chemotherapy, chronic pelvic pain, complex regional pain syndrome and related neuralgias. It has been shown in human patients as well as in animal models of neuropathic pain, that damage to primary afferent sensory neurons can lead to neuroma formation and spontaneous activity, as well as evoked activity in response to normally innocuous stimuli. [Carter, G.T. and B.S. Galer, *Advances in the management of neuropathic pain.* Physical Medicine and Rehabilitation Clinics of North America, 2001. **12**(2): p. 447-459]. The ectopic activity of normally silent sensory neurons is thought to contribute to the generation and maintenance of neuropathic pain. Neuropathic pain is generally assumed to be associated with an increase in sodium channel activity in the injured nerve. [Baker, M.D. and J.N. Wood, *Involvement of Na channels in pain pathways.* TRENDS in Pharmacological Sciences, 2001. **22**(1): p. 27-31].

Indeed, in rat models of peripheral nerve injury, ectopic activity in the injured nerve corresponds to the behavioral signs of pain. In these models, intravenous application of the sodium channel blocker and local anesthetic lidocaine can suppress the ectopic activity and reverse the tactile allodynia at concentrations that do not affect general behavior and motor function. [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain, 2000. **87**: p. 7-17]. These effective concentrations were similar to concentrations shown to be clinically efficacious in humans. [Tanelian, D.L. and W.G. Brose, *Neuropathic pain can be relieved by drugs that are use-dependent sodium channel blockers: lidocaine, carbamazepine and mexiletine.* Anesthesiology, 1991. **74**(5): p. 949-951]. In a placebo-controlled study, continuous infusion of lidocaine caused reduced pain scores in patients with peripheral nerve injury, and in a separate study, intravenous lidocaine reduced pain intensity associated with postherpetic neuralgia (PHN). [Mao, J. and L.L. Chen, *Systemic lidocaine for neuropathic pain relief.* Pain, 2000. **87**: p. 7-17. Anger, T., *et al.*, *Medicinal chemistry of neuronal voltage-gated sodium channel blockers.* Journal of Medicinal Chemistry, 2001. **44**(2): p. 115-137]. Lidoderm®, lidocaine applied in the form of a dermal patch, is currently the only FDA approved treatment for PHN. [Devers, A. and B.S. Galer, *Topical lidocaine patch relieves a variety of neuropathic pain conditions: an open-label study.* Clinical Journal of Pain, 2000. **16**(3): p. 205-208].

In addition to neuropathic pain, sodium channel blockers have clinical uses in the treatment of epilepsy and cardiac arrhythmias. Recent evidence from animal models suggests that sodium channel blockers may also be useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and in patients with multiple sclerosis (MS). [Clare, J. J. ; *et al.* And Anger, T., *et al.*].

International Patent Publication WO 00/57877 describes aryl substituted pyrazoles, imidazoles, oxazoles, thiazoles, and pyrroles and their uses as sodium channel blockers. International Patent Publication WO 01/68612 describes aryl substituted pyridines, pyrimidines, pyrazines and triazines and their uses as sodium channel blockers. International Patent Publication WO 99/32462 describes triazine compounds for the treatment for CNS disorders. However, there remains a need for novel compounds and compositions that therapeutically block neuronal sodium channels with less side effects and higher potency than currently known compounds.

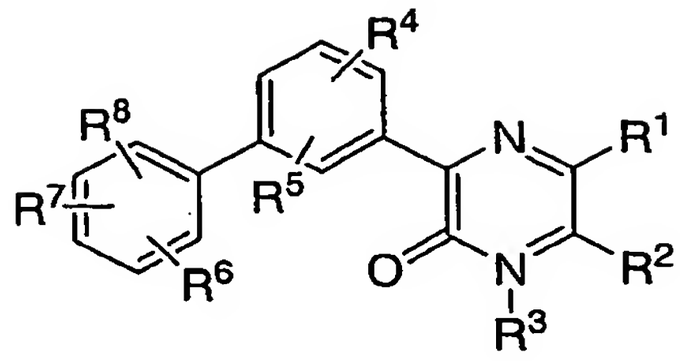
SUMMARY OF THE INVENTION

The present invention is directed to biaryl substituted pyrazinone compounds which are sodium channel blockers useful for the treatment of chronic and neuropathic pain. The compounds of the present invention are also useful for the treatment of other conditions, including urinary incontinence, itchiness, allergic dermatitis, and disorders of the CNS such as anxiety, depression, epilepsy, manic depression and bipolar disorder. This invention also provides pharmaceutical compositions comprising a compound of the present invention, either alone, or in combination with one or more therapeutically active compounds, and a pharmaceutically acceptable carrier.

This invention further comprises methods for the treatment of acute pain, chronic pain, visceral pain, inflammatory pain, neuropathic pain, urinary incontinence, itchiness, allergic dermatitis, and disorders of the CNS including, but not limited to, epilepsy, manic depression, depression, anxiety and bipolar disorder comprising administering the comounds and pharmaceutical compositions of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention comprises compounds represented by Formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R^1 and R^2 each independently is

(a) H,

(b) C_1-C_6-alkyl, optionally substituted with one or more substituents selected from the group consisting of: F, CF_3, OH, NR^aR^b, COOH, $CONR^aR^b$, $SO_2NR^aR^b$, $C(=NH)NH_2$, tetrazolyl, triazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl and piperazinyl,

(c) $-C(=O)R^a$, $COOR^a$, $CONR^aR^b$,

(d) $-C_0$-C_4-alkyl-C_1-C_4-perfluoroalkyl,

(e) NR^aR^b, $-N(COR^a)R^b$, $-N(SO_2R^a)R^b$, or

(f) tetrazolyl, triazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl or piperazinyl, any of which is optionally substituted with 1-3 substituents independently selected from the group consisting of: F, Cl, Br, I and CN;

R^a is

(a) H,

(b) C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from the group consisting of CF_3 and O-(C_1-C_4)alkyl,

(c) C_0-C_4-alkyl-(C_1-C_4)-perfluoroalkyl,

(d) NH_2,

(e) C_1-C_4-alkyl-phenyl, C_1-C_4-alkyl-pyridyl, or

(f) C_3-C_7-cycloalkyl, optionally substituted with one or more substituents selected from the group consisting of: F, Cl, Br, OH, -O-C_1-C_4-alkyl, and C_1-C_4-alkyl;

R^b is

(a) H, or

(b) C_1-C_6-alkyl;

R^3 is:

(a) H,

(b) -C_1-C_4-alkyl, optionally substituted with one or more substituents independently selected from the group consisting of: F, CF_3, Cl, N, OH, O-(C_1-C_4)alkyl, $S(O)_{0-2}$-(C_1-C_4)alkyl, O-$CONR^aR^b$, NR^aR^b, $N(R^a)CONR^aR^b$, $COOR^a$, CN, $CONR^aR^b$, $SO_2NR^aR^b$, $N(R^a)SO_2NR^aR^b$, -C(=NH)NH_2, tetrazolyl, triazolyl, imidazolyl, oxazolyl, oxadiazolyl, isooxazolyl, thiazolyl, furyl, thienyl, pyrazolyl, pyrrolyl, pyridyl, pyrimidinyl, pyrazinyl, phenyl, piperidinyl, morpholinyl, pyrrolidinyl and piperazinyl,
or R^a and R^b, together with N to which they are attached, may form a C_3-C_7-cycloalkyl or a C_3-C_7-heterocycloalkyl, wherein said cycloalkyl and heterocycloalkyl is optionally substituted with one or more substituents selected from the group consisting of: F, Cl, Br, OH, -O-C_1-C_4-alkyl, and C_1-C_4-alkyl,

(c) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,

(d) C_1-C_4-alkyl-C(=O)-R^a, -C_1-C_4-alkyl-C(=O)-C_1-C_4-perfluoroalkyl, or

(e) -C_1-C_4-alkyl-C_3-C_7-cycloalkyl, wherein said cycloalkyl is optionally substituted with one or more substituents selected from the group consisting of: F, Cl, Br, OH, -O-C_1-C_4-alkyl, and C_1-C_4-alkyl;

R^4 and R^5 each independently is:

(a) H,

(b) -C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from the group consisting of: F, CF_3 and -O-(C_1-C_4)alkyl,

(c) -O-C_0-C_6-alkyl, -O-phenyl, -O-C_1-C_4-alkyl-phenyl, -O-pyridyl, -O-C_1-C_4-alkyl-pyridyl, wherein phenyl and pyridyl are optionally substituted with 1-3 substituents independently selected from the group consisting of: F, Cl, Br, I and CN,

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, or

(e) F, Cl, Br, I; and

R^6, R^7 and R^8 each independently is:

(a) H,

(b) C_1-C_6-alkyl,

(c) -O- C_1-C_6-alkyl, optionally substituted with one or more substituents independently selected from the group consisting of: F and CF_3,

(d) -C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, -O-C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,

(e) -O-phenyl, -O-C_1-C_4-alkyl-phenyl, -O-pyridyl, -O-C_1-C_4-alkyl-pyridyl, wherein phenyl and pyridyl are optionally substituted with 1-3 substituents independently selected from the group consisting of: F, Cl, Br, I, and CN, or

(f) F, Cl, Br, I, -OR^a, phenyl or pyridyl, wherein phenyl and pyridyl are optionally substituted with one or more substituents independently selected from the group consisting of: F, Cl, Br, I and CN,

with the proviso that when R^6 and R^7 are present on adjacent carbon atoms, R^6 and R^7, together with the benzene ring to which they are attached, may form a bicyclic aromatic ring selected from the group consisting of: naphthyl, quinolinyl and benzothiazolyl, any aromatic ring of which is optionally substituted with 1-4 substituents independently selected from F, Cl, Br, I and CN.

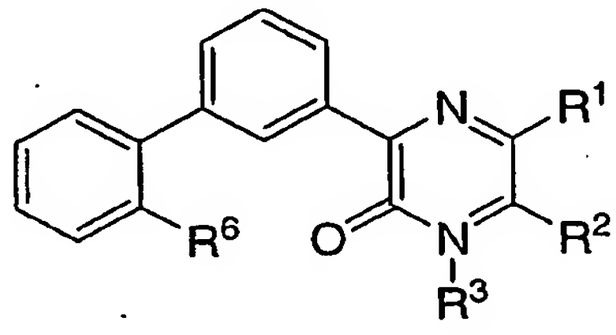
In one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

R^6 is other than H and is attached at the ortho position, and all other variables are as previously defined.

In an embodiment of this one aspect, the present invention provides a compound described by the chemical Formula (I), or a pharmaceutically acceptable salt thereof, wherein

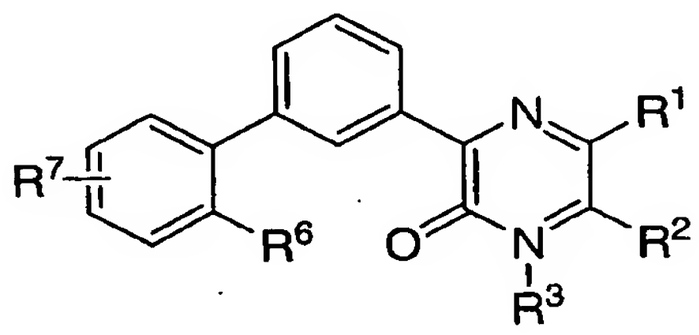
R^1 is H, $COOR^a$ or $CONR^aR^b$, and all other variables are as previously defined.

In a second aspect, the present invention provides sodium channel blockers described by the chemical Formula (I), or pharmaceutically acceptable salts thereof, which include compounds of the Formula Ia:



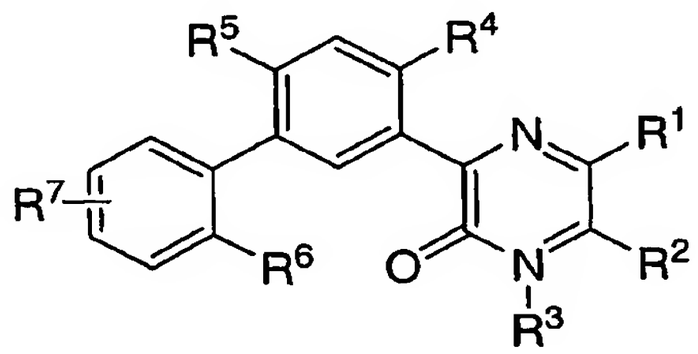
wherein
R^6 is OR^a or C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl, and all other variables are as previously defined.

In a third aspect, the present invention provides sodium channel blockers described by the chemical Formula (I), or pharmaceutically acceptable salts thereof, which include compounds of the Formula Ib:



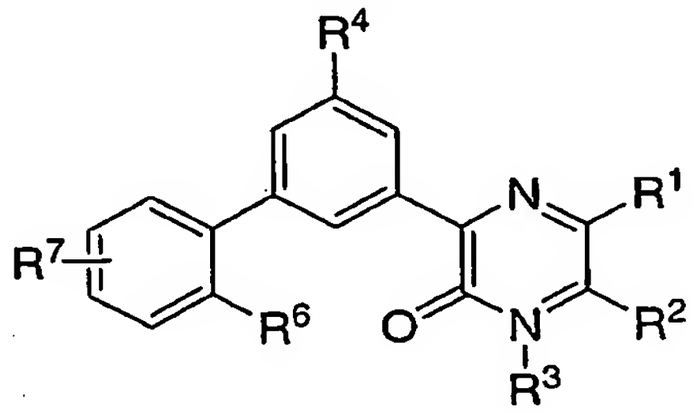
wherein
R^6 is OR^a or C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;
R^7 is H, F, Cl, Br or I; and all other variables are as previously defined.

In a fourth aspect, the present invention provides sodium channel blockers described by the chemical Formula (I), or pharmaceutically acceptable salts thereof, which include compounds of the Formula Ic:



wherein
R^4 and R^5 each independently is H, F, Cl, Br or I;
R^6 is OR^a or C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;
R^7 is H, F, Cl, Br or I; and all other variables are as previously defined.

In a fifth aspect, the present invention provides sodium channel blockers described by the chemical Formula (I), or pharmaceutically acceptable salts thereof, which include compounds of the Formula Id:



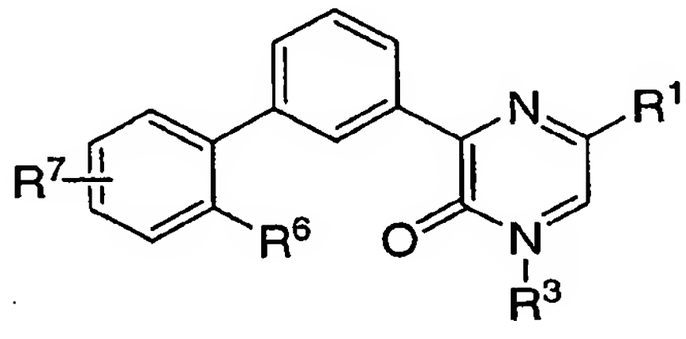
wherein

R^4 is F, Cl, Br or I;

R^6 is OR^a or C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl;

R^7 is H, F, Cl, Br or I; and all other variables are as previously defined.

In a sixth aspect, the present invention provides sodium channel blockers described by the chemical Formula (I), or pharmaceutically acceptable salts thereof, which include compounds of the Formula Ie:



wherein

R^1 is $CONH_2$;

R^6 is OR^a or C_0-C_4-alkyl-C_1-C_4-perfluoroalkyl,

R^7 is H or F, and all other variables are as previously defined.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, and alkynyl means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and

tert-butyl, pentyl, hexyl, and heptyl. "Alkenyl," "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, and 1,2,3,4-tetrahydronaphalene. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, and indenyl. The term "aryl" includes any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of aryl include phenyl, naphthyl, indanyl or biphenyl.

The term "cycloalkyloxy," unless specifically stated otherwise, includes a cycloalkyl group connected by a short C_{1-2}alkyl to the oxy connecting atom.

The term "C_{0-4}alkyl" includes alkyls containing 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

The term "hetero," unless specifically stated otherwise, includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a C_5-heterocycloalkyl is a five-member ring containing from 4 to no carbon atoms. Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, benzoxazolyl, isoxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuranyl, imidazolinyl, pyrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

The term "heteroC_{0-4}alkyl" means a heteroalkyl containing 3, 2, 1, or no carbon atoms. However, at least one heteroatom must be present. Thus, as an example, a heteroC_{0-4}alkyl having no carbon atoms but one N atom would be a -NH– if a bridging group and a $–NH_2$ if a terminal group. Analogous bridging or terminal groups are clear for an O or S heteroatom.

The term "amine," unless specifically stated otherwise, includes primary, secondary and tertiary amines.

The term "carbonyl," unless specifically stated otherwise, includes a C_{0-6}alkyl substituent group when the carbonyl is terminal.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "mammal" "mammalian" or "mammals" includes humans, as well as animals, such as dogs, cats, horses, pigs and cattle.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the alkyl and the aryl groups are optionally substituted. If only one of the multiple moieties is optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

The term "patient" includes mammalian subjects such as humans and animals. Accordingly, in addition to a human, a patient can be, for example, a dog, cat, horse, pig or cow.

Compounds described herein may contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers unless specifically stated otherwise.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereoisomers and optical isomers. The present invention includes all such possible diastereoisomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above chemical Formulas are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of the chemical Formulas and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other

pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N, N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, and tromethamine..

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. The pharmaceutical compositions of the present invention comprise compounds of the invention (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier, and optionally one or more additional therapeutic agents or adjuvants. Such additional therapeutic agents can include, for example, i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists, iv) sodium channel antagonists, v) NMDA receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) NK1 antagonists, viii) non-steroidal anti-inflammatory drugs ("NSAID"), ix) selective serotonin reuptake inhibitors ("SSRI") and/or selective serotonin and norepinephrine reuptake inhibitors ("SSNRI"), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, and xiv) neurontin (gabapentin). The instant compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

The present compounds and compositions are useful for the treatment of chronic, visceral, inflammatory and neuropathic pain syndromes. They are useful for the treatment of pain resulting from traumatic nerve injury, nerve compression or entrapment, postherpetic neuralgia, trigeminal neuralgia, and diabetic neuropathy. The present compounds and compositions are also useful for the treatment of chronic lower back pain, phantom limb pain, chronic pelvic pain, neuroma pain, complex regional pain syndrome, chronic arthritic pain and related neuralgias, and pain associated with cancer, chemotherapy, HIV and HIV treatment-induced neuropathy. Compounds of this invention may

also be utilized as local anesthetics. The instant compounds may also be useful in the treatment of disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia, frequent urination and urinary incontinence, including the prevention or treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. Compounds of this invention are useful for the treatment of irritable bowel syndrome and related disorders, as well as Crohn's disease.

The instant compounds have clinical uses for the treatment of epilepsy and partial and generalized tonic seizures. They are also useful for neuroprotection under ischaemic conditions caused by stroke or neural trauma and for treating multiple sclerosis. The present compounds are useful for the treatment of tachy-arrhythmias. Additionally, the instant compounds are useful for the treatment of neuropsychiatric disorders, including mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

The present compounds are also useful for the treatment of pruritis, dermatitis, allergic dermatitis, atopic dermatitis, itchiness, and itchy skin, including the treatment of itchy skin, atopic dermatitis, and allergic dermatitis in animals such as dogs and cats.

It will be appreciated that for the treatment of depression or anxiety, a compound of the present invention may be used in conjunction with other anti-depressant or anti-anxiety agents, such as norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), reversible inhibitors of monoamine oxidase (RIMAs), serotonin and noradrenaline reuptake inhibitors (SNRIs), α-adrenoreceptor antagonists, atypical anti-depressants, benzodiazepines, 5-HT_{1A} agonists or antagonists, especially 5-HT_{1A} partial agonists, neurokinin-1 receptor antagonists, corticotropin releasing factor (CRF) antagonists, and pharmaceutically acceptable salts thereof.

Further, it is understood that compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions and disorders, as well as to prevent other conditions and disorders associated with sodium channel activity.

Creams, ointments, jellies, solutions, or suspensions containing the instant compounds can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of inflammatory and neuropathic pain, or alternatively about 0.5mg to about 7g

per patient per day. For example, inflammatory pain may be effectively treated by the administration of from about 0.01mg to about 75mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Neuropathic pain may be effectively treated by the administration of from about 0.01mg to about 125mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 5.5g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors. Such patient-related factors include the age, body weight, general health, sex, and diet of the patient. Other factors include the time and route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

In practice, the compounds of the invention, or pharmaceutically acceptable salts thereof, can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compounds of the invention, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I, Ia, Ib, Ic or Id. The compounds of the invention, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all

cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage, and thus should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, and dusting powder. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented of the invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid, such as, for example, where the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, and preservatives (including anti-oxidants). Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound of the invention, or pharmaceutically acceptable salts thereof, can also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to block sodium channels. Accordingly, an aspect of the invention is the treatment and prevention in mammals of conditions that are amenable to amelioration through blockage of neuronal sodium channels by administering an effective amount of a compound of this invention. Such conditions include, for example, acute pain, chronic pain, visceral pain, inflammatory pain and neuropathic pain. The instant compounds and compositions are useful for treating and preventing the conditions recited herein, including acute pain, chronic pain, visceral pain, inflammatory pain, urinary incontinence, itchiness, allergic dermatitis, pruritis and neuropathic pain, in humans and non-human mammals such as dogs and cats. It is understood that the treatment of mammals other than humans refers to the treatment of clinical conditions in non-human mammals that correlate to the conditions recited herein.

Further, as described above, the instant compounds can be utilized in combination with one or more therapeutically active compounds. In particular, the inventive compounds can be advantageously used in combination with i) opiate agonists or antagonists, ii) calcium channel antagonists, iii) 5HT receptor agonists or antagonists, including 5-HT_{1A} agonists or antagonists, and 5-HT_{1A} partial agonists, iv) sodium channel antagonists, v) N-methyl-D-aspartate (NMDA) receptor agonists or antagonists, vi) COX-2 selective inhibitors, vii) neurokinin receptor 1 (NK1) antagonists, viii) non-steroidal anti-inflammatory drugs (NSAID), ix) selective serotonin reuptake inhibitors (SSRI) and/or selective serotonin and norepinephrine reuptake inhibitors (SSNRI), x) tricyclic antidepressant drugs, xi) norepinephrine modulators, xii) lithium, xiii) valproate, xiv) norepinephrine reuptake inhibitors, xv) monoamine oxidase inhibitors (MAOIs), xvi) reversible inhibitors of monoamine oxidase (RIMAs), xvii)□-adrenoreceptor antagonists, xviii) atypical anti-depressants, xix) benzodiazepines, xx) corticotropin releasing factor (CRF) antagonists, xxi) neurontin (gabapentin), xxii) anticholinergic agents, and xxiii) muscarinic receptor antagonists.

The abbreviations used herein have the following meanings (abbreviations not shown here have their meanings as commonly used unless specifically stated otherwise): Ac (acetyl), AIBN (2,2'-azobis(isobutyronitrile)), BINAP (1,1'-bi-2-naphthol), Bn (benzyl), CAMP (cyclic adenosine-3',5'-monophosphate), DAST ((diethylamino)sulfur trifluoride), DEAD (diethyl azodicarboxylate), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DIBAL (diisobutylaluminum hydride), DMAP (4-(dimethylamino)pyridine), DMF (N,N-dimethylformamide), Dppf (1,1'-bis(diphenylphosphino)-ferrocene), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), Et3N (triethylamine), GST (glutathione transferase), HMDS (Hexamethyldisilazide), LDA (lithium diisopropylamide), m-CPBA (metachloroperbenzoic acid), MMPP (monoperoxyphthalic acid), MPPM (monoperoxyphthalic acid), Ms (methanesulfonyl; mesyl; or SO2Me), MsO (methanesulfonate or mesylate), NBS (N-bromo succinimide), NSAID (non-steroidal anti-inflammatory drug), o-Tol (ortho-tolyl), OXONE® (2KHSO5•KHSO4•K2SO4), PCC (pyridinium chlorochromate), Pd2(dba)3 (Bis(dibenzylideneacetone) palladium(0)), PDC (pyridinium dichromate), PDE (Phosphodiesterase), Ph (Phenyl), Phe (Benzenediyl), PMB (para-methoxybenzyl), Pye (Pyridinediyl), r.t. or RT (room temperature), Rac (Racemic), SAM (aminosulfonyl; sulfonamide or SO2NH2), SEM (2-(trimethylsilyl)ethoxymethoxy), SPA (scintillation proximity assay), TBAF (tetra-n-butylammonium fluoride), Th (2- or 3-thienyl), TFA (trifluoroacetic acid), TFAA (trifluoroacetic acid anhydride), THF (Tetrahydrofuran), Thi (Thiophenediyl), TLC (thin layer chromatography), TMS-CN (trimethylsilyl cyanide), TMSI (trimethylsilyl iodide), Tz (1H (or 2H)-tetrazol-5-yl), XANTPHOS (4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene), C3H5 (Allyl), Me (methyl), Et (ethyl), n-Pr (normal

propyl), i-Pr (isopropyl), n-Bu (normal butyl), i-Butyl (isobutyl), s-Bu (secondary butyl), t-Bu (tertiary butyl), c-Pr (cyclopropyl), c-Bu (cyclobutyl), c-Pen (cyclopentyl), c-Hex (cyclohexyl).

The following *in vitro* and *in vivo* assays were used in assessing the biological activity of the instant compounds.

Compound Evaluation (*in vitro* assay):

The identification of inhibitors of the sodium channel is based on the ability of sodium channels to cause cell depolarization when sodium ions permeate through agonist-modified channels. In the absence of inhibitors, exposure of an agonist-modified channel to sodium ions will cause cell depolarization. Sodium channel inhibitors will prevent cell depolarization caused by sodium ion movement through agonist-modified sodium channels. Changes in membrane potential can be determined with voltage-sensitive fluorescence resonance energy transfer (FRET) dye pairs that use two components, a donor coumarin (CC_2DMPE) and an acceptor oxanol (Di$SBAC_2$(3)). Oxanol is a lipophilic anion and distributes across the membrane according to membrane potential. In the presence of a sodium channel agonist, but in the absence of sodium, the inside of the cell is negative with respect to the outside, oxanol is accumulated at the outer leaflet of the membrane and excitation of coumarin will cause FRET to occur. Addition of sodium will cause membrane depolarization leading to redistribution of oxanol to the inside of the cell, and, as a consequence, to a decrease in FRET. Thus, the ratio change (donor/acceptor) increases after membrane depolarization. In the presence of a sodium channel inhibitor, cell depolarization will not occur, and therefore the distribution of oxanol and FRET will remain unchanged.

Cells stably transfected with the PN1 sodium channel (HEK-PN1) were grown in polylysine-coated 96-well plates at a density of ca. 140,000 cells/well. The media was aspirated, and the cells were washed with PBS buffer, and incubated with 100µl of 10µm CC_2-DMPE in 0.02% pluronic acid. After incubation at 25°C for 45min, media was removed and cells were washed 2x with buffer. Cells were incubated with 100µl of Di$SBAC_2$(3) in TMA buffer containing 20µm veratridine, 20nm brevetoxin-3, and test sample. After incubation at 25°C for 45min in the dark, plates were placed in the VIPR instrument, and the fluorescence emission of both CC_2-DMPE and Di$SBAC_2$(3) recorded for 10s. At this point, 100µl of saline buffer was added to the wells to determine the extent of sodium-dependent cell depolarization, and the fluorescence emission of both dyes recorded for an additional 20s. The ratio CC_2-DMPE/Di$SBAC_2$(3), before addition of saline buffer equals 1. In the absence of inhibitors, the ratio after addition of saline buffer is > 1.5. When the sodium channel has been completely inhibited by either a known standard or test compound, this ratio remains at 1. It is possible, therefore, to titrate the activity of a sodium channel inhibitor by monitoring the concentration-dependent change in fluorescence ratio.

Electrophysiological Assays (*In Vitro* assays):

Cell preparation: A HEK-293 cell line stably expressing the PN1 sodium channel subtype was established in-house. The cells were cultured in MEM growth media (Gibco) with 0.5mg/Ml G418, 50 units/Ml Pen/Strep and 1Ml heat-inactivated fetal bovine serum at 37°C and 10% CO_2. For electrophysiological recordings, cells were plated on 35mm dishes coated with poly-D-lysine.

Whole-cell recordings: HEK-293 cells stably expressing the PN1 sodium channel subtype were examined by whole cell voltage clamp (Hamill, *et al.* Pfluegers Archives 391:85-100 (1981)) using an EPC-9 amplifier and Pulse software (HEKA Electronics, Lamprecht, Germany). Experiments were performed at room temperature. Electrodes were fire-polished to resistances of 2-4 MΩ. Voltage errors were minimized by series resistance compensation, and the capacitance transient was canceled using the EPC-9's built-in circuitry. Data were acquired at 50 kHz and filtered at 7-10 kHz. The bath solution consisted of 40 mM NaCl, 120 mM NMDG Cl, 1 mM KCl, 2.7 mM $CaCl_2$, 0.5 mM $MgCl_2$, 10 mM NMDG HEPES, Ph 7.4, and the internal (pipet) solution contained 110 mM Cs-methanesulfonate, 5 mM NaCl, 20mM CsCl, 10mM CsF, 10 mM BAPTA (tetra Cs salt), 10 mM Cs HEPES, Ph 7.4.

The following protocols were used to estimate the steady-state affinity of compounds for the resting and inactivated state of the channel (K_r and K_i, respectively):

1. 8ms test-pulses to depolarizing voltages from –60Mv to +50Mv from a holding potential of –90Mv were used to construct current-voltage relationships (IV-curves). A voltage near the peak of the IV-curve (typically –10 or 0 Mv) was used as the test-pulse voltage throughout the remainder of the experiment.

2. Steady-state inactivation (availability) curves were constructed by measuring the current activated during an 8ms test-pulse following 10s conditioning pulses to potentials ranging from –120Mv to –10Mv.

3. Compounds were applied at a holding potential at which 20-50% of the channels was inactivated and sodium channel blockage was monitored during 8ms test pulses at 2s intervals.

4. After the compounds equilibrated, the voltage-dependence of steady-state inactivation in the presence of compound was determined according to protocol 2) above. Compounds that block the resting state of the channel decrease the current elicited during test-pulses from all holding potentials, whereas compounds that primarily block the inactivated state shift the mid-point of the steady-state inactivation curve. The maximum current at negative holding potentials (I_{max}) and the difference in the mid-points of the steady-state inactivation curves (ΔV) in control and in the presence of a compound were used to calculate K_r and K_i using the following equations:

$$K_r = \frac{[Drug] * I_{Max,Drug}}{I_{Max,Control} - I_{Max,Drug}}$$

$$K_i = \frac{[Drug]}{\left(1 + \frac{[Drug]}{K_r}\right) * e^{\frac{-\Delta V}{k}} - 1}$$

In cases where the compound did not affect the resting state, K_i was calculated using the following equation:

$$K_i = \frac{[Drug]}{e^{\frac{-\Delta V}{k}} - 1}$$

Rat Formalin Paw test (*in vivo* assay):

Compounds were assessed for their ability to inhibit the behavioral response evoked by a 50Ml injection of formalin (5%). A metal band was affixed to the left hind paw of male Sprague-Dawley rats (Charles River, 200-250g) and each rat was conditioned to the band for 60min within a plastic cylinder (15cm diameter). Rats were dosed with either vehicle or a test compound either before (local) or after (systemic) formalin challenge. For local administration, compounds were prepared in a 1:4:5 vehicle of ethanol, PEG400 and saline (EPEGS) and injected subcutaneously into the dorsal surface of the left hind paw 5min prior to formalin. For systemic administration, compounds were prepared in either a EPEGS vehicle or a Tween80 (10%)/sterile water (90%) vehicle and were injected i.v. (via the lateral tail vein 15min after formalin) or p.o. (60min before formalin). The number of flinches was counted continuously for 60min using an automated nociception analyzer (UCSD Anesthesiology Research, San Diego, CA). Statistical significance was determined by comparing the total flinches detected in the early (0-10min) and late (11-60min) phase with an unpaired t-test.

***In vivo* assay using Rat CFA model:**

Unilateral inflammation was induced with a 0.2 ml injection of complete Freund's adjuvant (CFA: Mycobacterium tuberculosis, Sigma; suspended in an oil/saline (1:1) emulsion; 0.5mg Mycobacterium/Ml) in the plantar surface of the left hindpaw. This dose of CFA produced significant hind paw swelling but the animals exhibited normal grooming behavior and weight gain over the course

of the experiment. Mechanical hyperalgesia was assessed 3 days after tissue injury using a Randall-Selitto test. Repeated Measures ANOVA, followed by Dunnett's Post Hoc test.

SNL: Mechanical Allodynia (*in vivo* assay):

Tactile allodynia was assessed with calibrated von Frey filaments using an up-down paradigm before and two weeks following nerve injury. Animals were placed in plastic cages with a wire mesh floor and allowed to acclimate for 15min before each test session. To determine the 50% response threshold, the von Frey filaments (over a range of intensities from 0.4 to 28.8g) were applied to the mid-plantar surface for 8s, or until a withdrawal response occurred. Following a positive response, an incrementally weaker stimulus was tested. If there was no response to a stimulus, then an incrementally stronger stimulus was presented. After the initial threshold crossing, this procedure was repeated for four stimulus presentations per animal per test session. Mechanical sensitivity was assessed 1 and 2 hr post oral administration of the test compound.

The compounds described in this invention displayed sodium channel blocking activity of from about <0.1mM to about <50mM in the *in vitro* assays described above. It is advantageous that the compounds display sodium channel blocking activity of <5mM in the *in vitro* assays. It is more advantageous that the compounds display sodium channel blocking activity of <1mM in the *in vitro* assays. It is even more advantageous that the compounds display sodium channel blocking activity of <0.5mM in the *in vitro* assays. It is still more advantageous that the compounds display sodium channel blocking activity of <0.1mM in the *in vitro* assays.

The present compounds can be prepared according to the general Schemes provided below as well as the procedures provided in the Examples. The following Schemes and Examples further describe, but do not limit, the scope of the invention.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions: All operations were carried out at room or ambient temperature; that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. When given, yields are for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in

parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. Broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations are used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), ml (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

Methods of Synthesis

Compounds of the present invention can be prepared according to the Schemes provided below as well as the procedures provided in the Examples. The substituents are the same as in the above Formulas except where defined otherwise or otherwise apparent to the ordinary skilled artisan.

The novel compounds of the present invention can be readily synthesized using techniques known to those skilled in the art, such as those described, for example, in Advanced Organic Chemistry, March, 4th Ed., John Wiley and Sons, New York, NY, 1992; Advanced Organic Chemistry, Carey and Sundberg, Vol. A and B, 3rd Ed., Plenum Press, Inc., New York, NY, 1990; Protective groups in Organic Synthesis, Green and Wuts, 2nd Ed., John Wiley and Sons, New York, NY, 1991; Comprehensive Organic Transformations, Larock, VCH Publishers, Inc., New York, NY, 1988; Handbook of Heterocyclic Chemistry, Katritzky and Pozharskii, 2nd Ed., Pergamon, New York, NY, 2000 and references cited therein. The starting materials for the present compounds may be prepared using standard synthetic transformations of chemical precursors that are readily available from commercial sources, including Aldrich Chemical Co. (Milwaukee, WI); Sigma Chemical Co. (St. Louis, MO); Lancaster Synthesis (Windham, N.H.); Ryan Scientific (Columbia, S. C.); Maybridge (Cornwall, UK); Matrix Scientific (Columbia, S. C.); Arcos, (Pittsburgh, PA) and Trans World Chemicals (Rockville, MD).

The procedures described herein for synthesizing the compounds may include one or more steps of protecting group manipulations and of purification, such as, recrystallization, distillation, column chromatography, flash chromatography, thin-layer chromatography (TLC), radial chromatography and high-pressure chromatography (HPLC). The products can be characterized using various techniques well known in the chemical arts, including proton and carbon-13 nuclear magnetic resonance (^{1}H and ^{13}C NMR), infrared and ultraviolet spectroscopy (IR and UV), X-ray crystallography, elemental analysis and HPLC and mass spectrometry (LC-MS). Methods of protecting group manipulation, purification, structure identification and quantification are well known to one skilled in the art of chemical synthesis.

Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents are aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile), ketones (e.g, 2-butanone, dithyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), dimethyl formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases are, generally, alkali metal

hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, Cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-bultyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethylamine, piperidine, N-methyl piperidine, morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

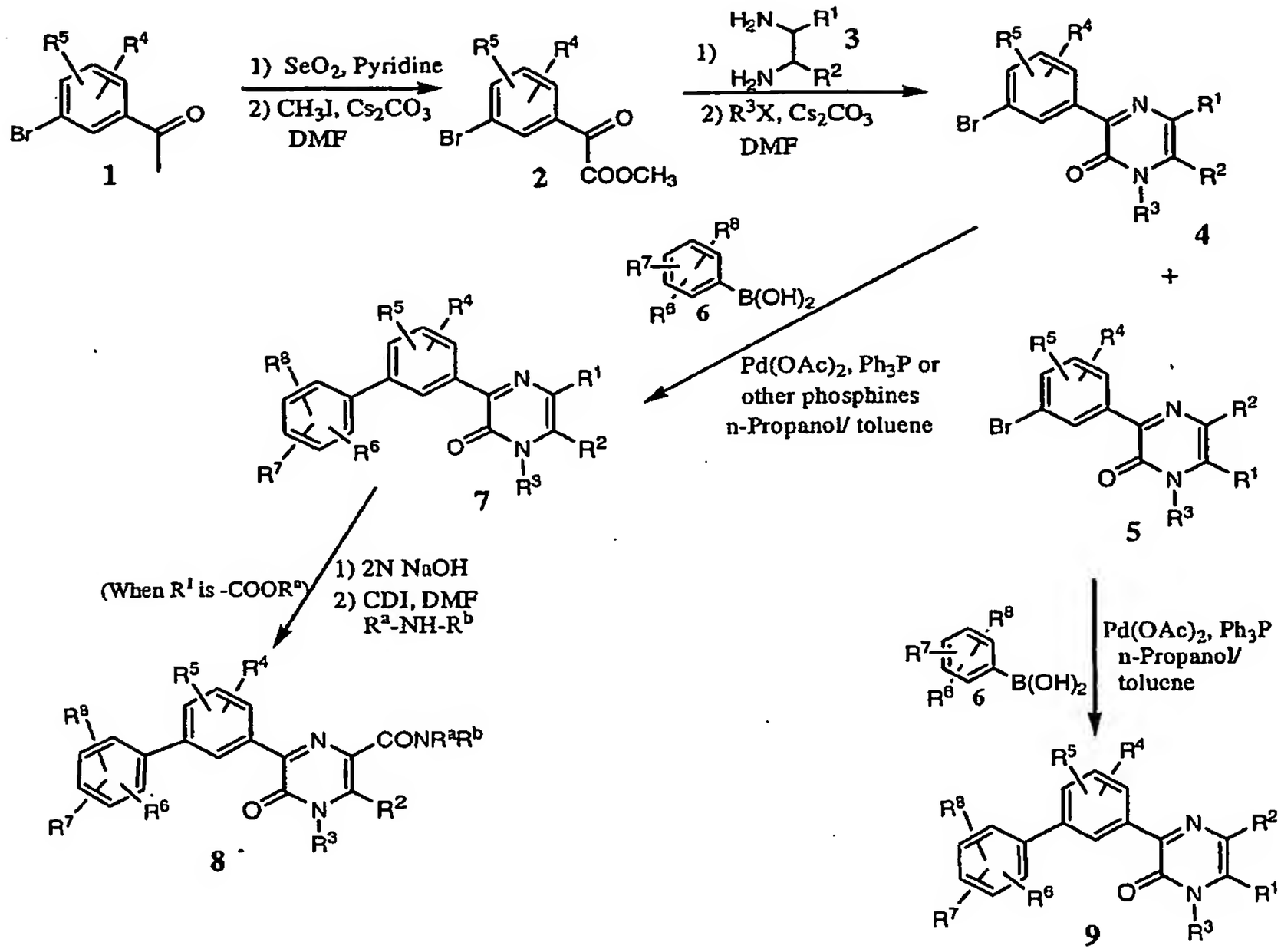
As described previously, in preparing the compositions for oral dosage form, any of the usual pharmaceutical media can be employed. For example, in the case of oral liquid preparations such as suspensions, elixirs and solutions, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used; or in the case of oral solid preparations such as powders, capsules and tablets, carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be included. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. In addition to the common dosage forms set out above, controlled release means and/or delivery devices may also be used in administering the instant compounds and compositions.

It is understood that the functional groups present in compounds described in the Schemes below can be further manipulated, when appropriate, using the standard functional group transformation techniques available to those skilled in the art, to provide desired compounds described in this invention.

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

Pyrazinone compounds of the present invention can be prepared as outlined in the following Schemes and Examples. Alternatively, the instant compounds can be prepared by adapting the methods described by Taylor, Takahashi and Kobayshi (Heterocycles **1996**, 43(2), 437-442), and Beccallie and Marchesini (Synthesis, **1991**, 861-862).

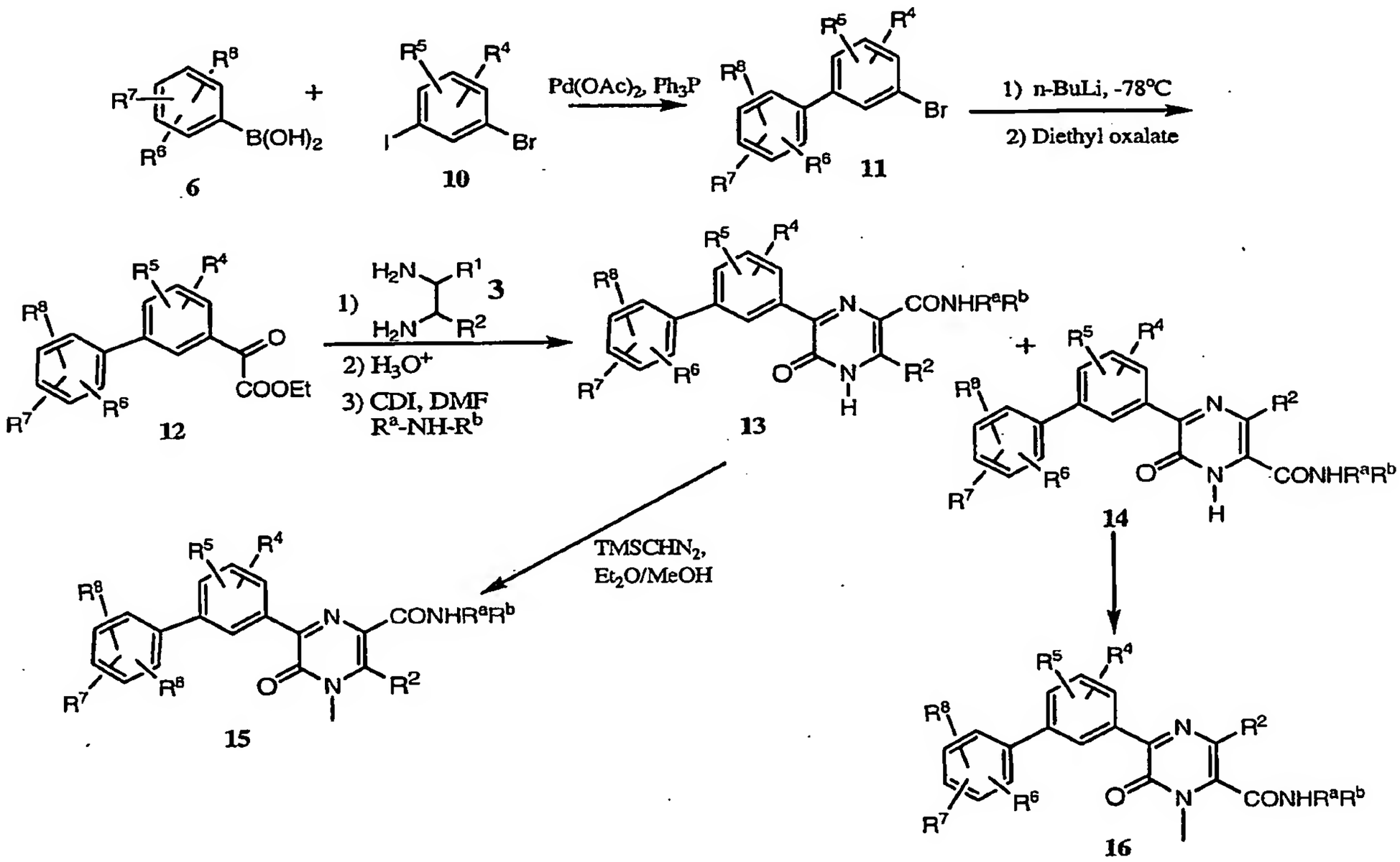
Scheme 1



An appropriate bromo or iodo acetophenone **1** can be oxidized with SeO_2 using the conditions described by Sakamoto, T. *et al.* [*Chem Pharm. Bull.* 28: 571-577(1980)] to provide the corresponding carboxylic acid, which without isolation can then be converted into the corresponding α-ketoester **2**. Reaction of **2** with an appropriate diamine **3**, optionally followed by capping of the NH group through N-alkylation, can provide a regioisomeric mixture of pyrazinones **4** and **5**. Separation of the regioisomers **4** and **5** by chromatography, followed by a Pd-catalyzed cross-coupling Suzuki reaction [Huff, B. et al., *Org. Synth.* 75: 53-60 (1997); Goodson, F. E. et al. *Org. Synth.* 75: 61-68 (1997)] of these individual isomers with an appropriately substituted aryl boronic acid **6** provides biphenyl pyrazinones **7** and **9.** When R^1in **7** is a carboxylic acid ester (R^1 = COOR), it can be hydrolyzed to provide the corresponding carboxylic acid (R^1 = COOH), which can be then treated with an appropriate amine R^a-NH-R^b in the presence of an appropriate carboxylic acid activating agent, such as carbonyl-di-imidazole (CDI) to provide the amide **8**. Alternatively, the ester **7** can be treated with excess ammonia in a polar

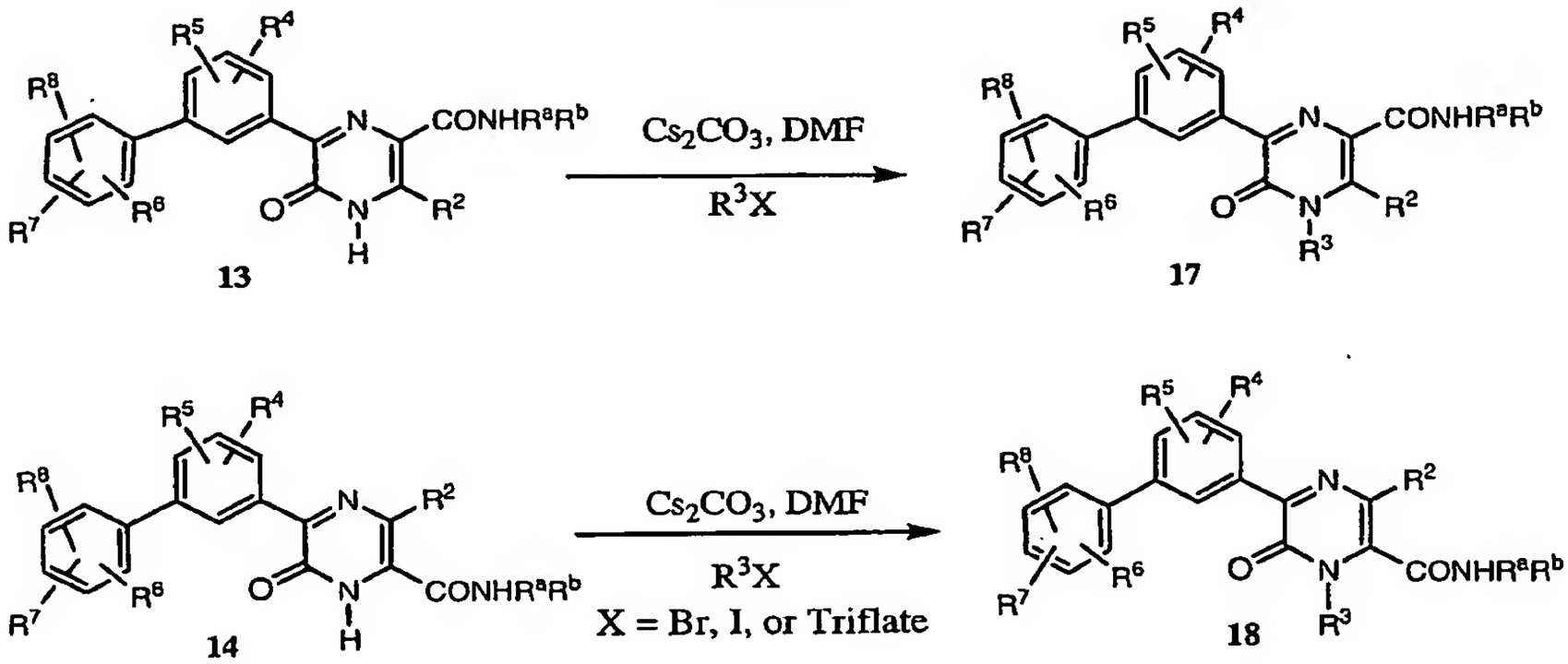
solvent, such as methanol, to provide the corresponding primary amide 8 (where R^a=R^b=H). The pyrazinone regioisomer **9** also can be converted into appropriate amide derivatives employing the chemistry described above.

Scheme 2



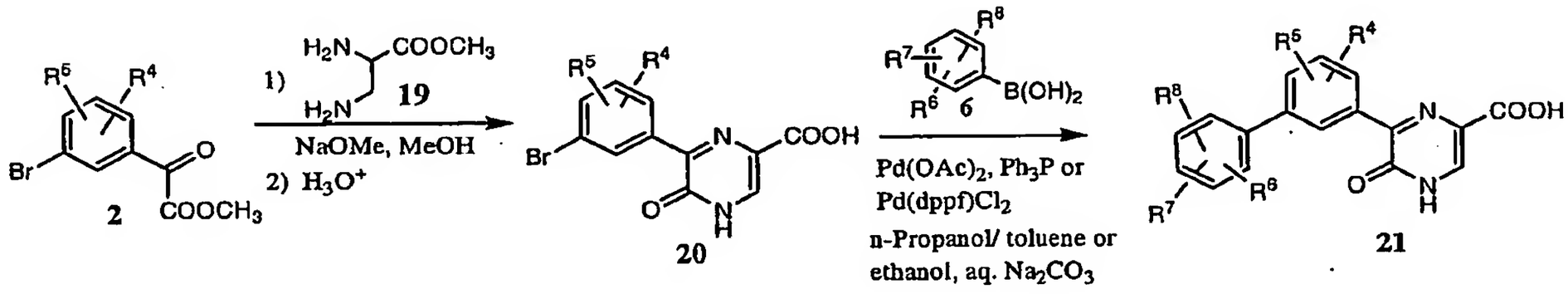
In an alternative approach to Scheme 1, the boronic acid **6** can be coupled with an appropriately substituted 3-iodo bromobenzene **10** to provide the biphenyl **11**, which can be then treated with n-BuLi followed by diethyloxalate to provide the α-ketoester **12**. Reaction of **12** with an appropriate diamine **3** followed by acid hydrolysis and amidation, as shown in Scheme 1, provides a mixture of pyrazinone amides **13** and **14**. Separation of the regioisomers **13** and **14** followed by treatment with $TMSCHN_2$ provides the N-methyl pyrazinones **15** and **16**.

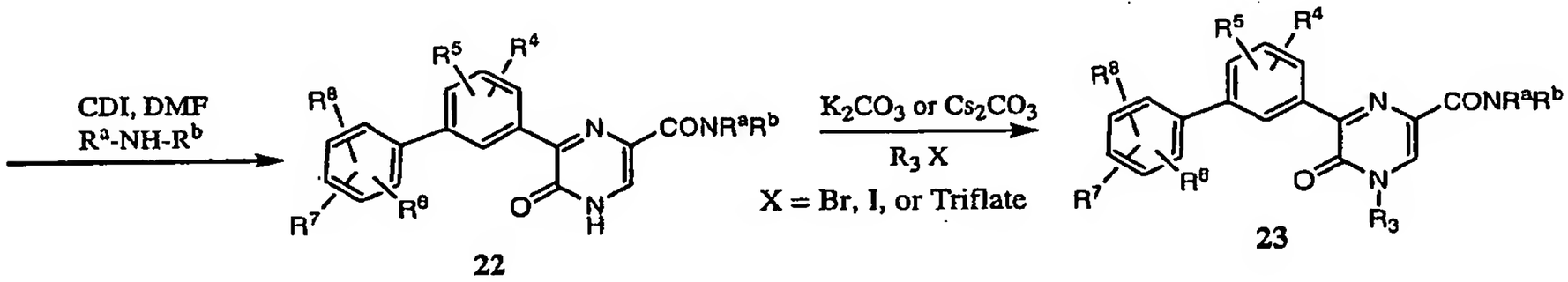
Scheme 3



The pyrazinones **13** and **14** can be also alkylated with other appropriate alkylating agents to provide pyrazinones **17** and **18**.

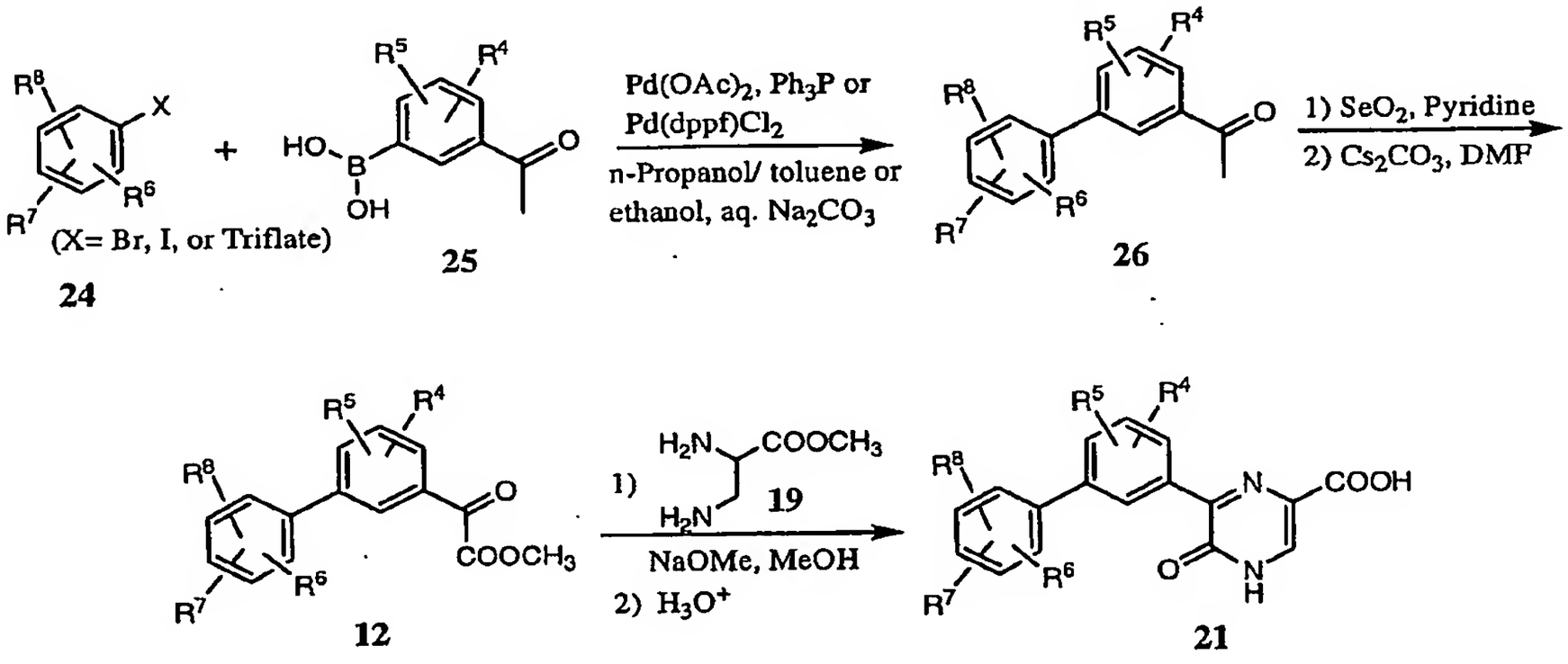
Scheme 4





In another approach, as described in Scheme 4, an appropriately substituted ketoester **2** can be condensed with methyl diaminopropionate (**19**) to provide the pyrazinone acid **20**, which can be condensed with an appropriate aryl boronic acid **6** to provide the corresponding biphenyl pyrazinone carboxylic acid **21**. The pyrazinone carboxamides **22** and **23** can be prepared from the carboxylic acid **21** as described in Scheme 4.

Scheme 5

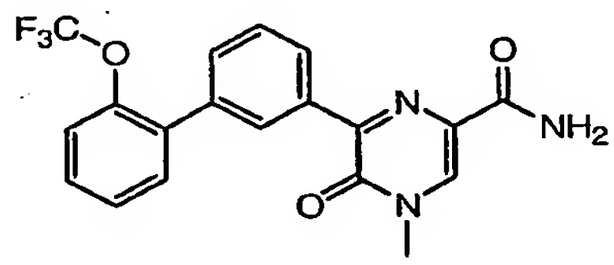


The pyrazinone carboxylic acid **21** can also be synthesiszed using an alternative approach outlined in Scheme 5. The aryl halide (or triflate) **24** can be coupled with an appropriately substituted aryl boronic acid **25** under Suzuki conditions to provide the corresponding biphenyl methyl ketone **26**, which can be oxidized to produce the desired ketoester **12**.

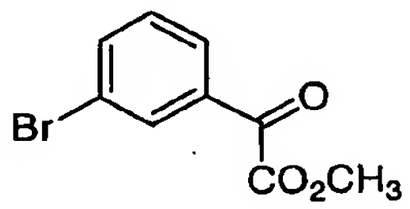
Appropriate solvents are those which will at least partially dissolve one or all of the reactants and will not adversely interact with either the reactants or the product. Suitable solvents include aromatic hydrocarbons (e.g, toluene, xylenes), halogenated solvents (e.g, methylene chloride, chloroform, carbontetrachloride, chlorobenzenes), ethers (e.g, diethyl ether, diisopropylether, tert-butyl methyl ether, diglyme, tetrahydrofuran, dioxane, anisole), nitriles (e.g, acetonitrile, propionitrile),

ketones (e.g, 2-butanone, diethyl ketone, tert-butyl methyl ketone), alcohols (e.g, methanol, ethanol, n-propanol, iso-propanol, n-butanol, t-butanol), dimethyl formamide (DMF), dimethylsulfoxide (DMSO) and water. Mixtures of two or more solvents can also be used. Suitable bases include alkali metal hydroxides, alkaline earth metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, and calcium hydroxide; alkali metal hydrides and alkaline earth metal hydrides such as lithium hydride, sodium hydride, potassium hydride and calcium hydride; alkali metal amides such as lithium amide, sodium amide and potassium amide; alkali metal carbonates and alkaline earth metal carbonates such as lithium carbonate, sodium carbonate, cesium carbonate, sodium hydrogen carbonate, and cesium hydrogen carbonate; alkali metal alkoxides and alkaline earth metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and magnesium ethoxide; alkali metal alkyls such as methyllithium, n-butyllithium, sec-butyllithium, t-bultyllithium, phenyllithium, alkyl magnaesium halides, organic bases such as trimethylamine, triethylamine, triisopropylamine, N,N-diisopropylethylamine, piperidine, N-methyl piperidine, morpholine, N-methyl morpholine, pyridine, collidines, lutidines, and 4-dimethylaminopyridine; and bicyclic amines such as DBU and DABCO.

EXAMPLE 1



Step 1: Preparation of:



A 100-ml round-bottom flask fitted with a stirbar, condenser, and septum was flushed with N_2 and charged with 3-bromoacetophenone (2.50 g) and anhydrous pyridine (20 mL), followed by selenium dioxide (2.8 g). The reaction mixture was heated to 100 °C. After one hour, the reaction was cooled to room temperature and pyridine was distilled off under reduced pressure. The resulting thick oil was partitioned between 50 ml 1N HCl and 50 ml EtOAc. The aqueous phase was extracted once more

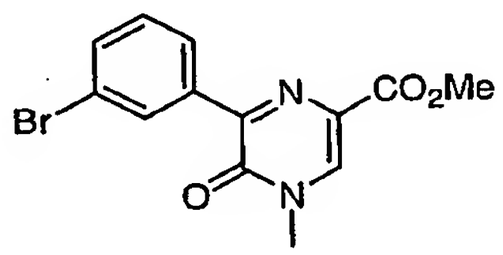
with 50 ml EtOAc, and the combined organic phase was dried over sodium sulfate and concentrated *in vacuo*. The resulting crude acid was azeotroped with 10 ml of anhydrous toluene.

To a 100-ml round-bottom flask containing the crude acid were added anhydrous DMF (20 ml), Cs_2CO_3 (4.11 g), and methyl iodide (3.58 g) sequentially. The mixture was heated at 40 °C for 1 hour under N_2, cooled to room temperature, diluted with 200 ml saturated NH_4Cl solution, and extracted two times with 200 ml EtOAc/hexanes (1/1). The combined organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel (25% EtOAc/hexanes) to provide the desired product.

^1H NMR ($CDCl_3$): 8.22 (s, 1H), 8.01 (d, J=8 Hz, 1H), 7.83 (d, J=8 Hz, 1H), 7.44 (t, J=8 Hz, 1H), 4.0 (s, 3H)

MS: m/e 243/245 $(M+1)^+$

Step 2: Preparation of



A 50-ml round-bottom flask fitted with a stirbar and septum was flushed with N_2 and charged with the keto methyl ester from Step1 (0.500 g), anhydrous methanol (10 mL), and methyl 2,3-diaminopropionate (0.772 g) [prepared from 2,3-diaminopropionic acid, commercially available from Sigma-Aldrich]. To the resulting mixture (a white suspension) was added sodium methoxide solution (3.4 ml, 25% w/w) dropwise over 5 min. The yellow reaction mixture thus obtained was stirred at room temperature under air for 30 min before being concentrated *in vacuo*. The resulting yellow solid was acidified with 50 ml 1N HCl solution and extracted (2 times) with 50 ml EtOAc. The combined organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude pyrazinone carboxylic acid thus obtained was dried under vacuum and then carried onto the next reaction.

To a solution of the crude pyrazinone carboxylic acid in anhydrous DMF (5 ml) were added Cs_2CO_3 (0.652 g), and methyl iodide (0.568 g) sequentially, and the mixture was heated to 40 °C for 1 hour. The reaction was then cooled to room temperature, diluted with 50 ml saturated NH_4Cl solution, and extracted (2 times) with 50 ml EtOAc. The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give a regioisomeric mixture of N-methyl pyrazinone. The isomers were

separated by column chromatography using silica gel (50-75% EtOAc/hexanes) to give regioisomer 1 N-methyl pyrazinone methyl ester.

^{1}H NMR ($CDCl_3$): 8.54 (t, J=2 Hz, 1H), 8.34 (d, J=8 Hz, 1H), 8.20 (s, 1H), 7.60 (d, J=8 Hz, 1H), 7.34 (t, J= 8 Hz, 1H), 3.98 (s, 3H), 3.69 (s, 3H)

MS: m/e 323/325 $(M+1)^+$

regioisomer 2: ^{1}H NMR ($CDCl_3$): 8.57 (t, J=2 Hz, 1H), 8.38 (d, J=8 Hz, 1H), 8.04 (s, 1H), 7.60 (d, J=8 Hz, 1H), 7.34 (t, J= 8 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 3H)

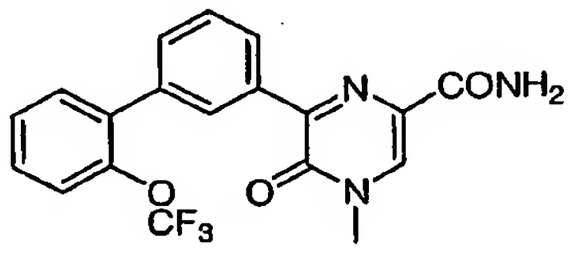
MS: m/e 323/325 $(M+1)^+$

Step 3: 2-(Trifluoromethoxy)phenylboronic acid:

n-Butyllithium (5.9 ml, 9.5 mmol) was added to a solution of 1-bromo-2-(trifluoromethoxy)benzene (2 g, 8.2 mmol) in tetrahydrofuran (28 ml) at –78°C and stirred for 45 minutes. Triisopropyl borate (2.58 ml, 11.1 mmol) was added dropwise to the reaction mixture and the solution was slowly brought to room temperature over 16 hours. The reaction mixture was quenched with water, made basic with 2N NaOH and extracted with ethyl acetate. The aqueous solution was acidified with 2N HCl, stirred for 1 hour at room temperature and extracted into ethyl acetate. The organic layer was washed with water, brine solution and dried over sodium sulfate. It was filtered and concentrated to give the product (1.10 g, 65%) as a white solid.

^{1}HNMR ($CDCl_3$)(δ, ppm): 7.96 (dd, *J*= 7.2, 1.6 Hz, 1 H), 7.53 (ddd, *J* = 9.1, 7.3, 1.8 Hz, 1 H), 7.38 (td, *J* = 7.3, 0.7 Hz, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 5.25 (br s, 2H). MS (M+H): 206.9.

Step 4: Preparation of



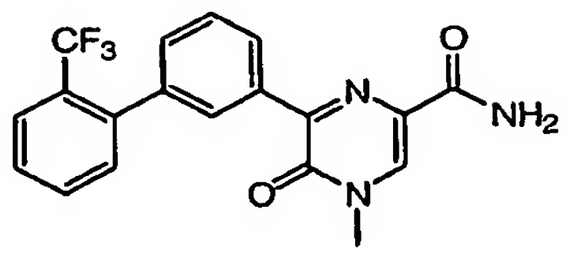
A 10-ml round-bottom flask with a stirbar was charged with aryl bromide from Step 2 (0.08 g) and 2-(trifluoromethoxy) phenyl boronic acid from Step 3 (0.153 g), followed by KF (0.086 g), and anhydrous dioxane (1 ml). Then $Pd(OAc)_2$ (0.011 g) and 2-(dicyclohexylphosphino)biphenyl (0.035 g) were added sequentially and the mixture was heated to 100 °C for 2 hours. After being cooled to room temperature, the mixture was diluted with 10 ml saturated NH_4Cl and extracted with 10 ml EtOAc/hexanes (1/1) twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The

crude mixture was purified by column chromatography on silica gel (50% EtOAc/hexanes) to give pure desired biphenyl pyrazinone compound.

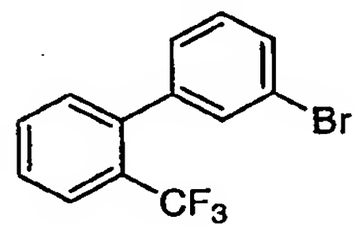
The methyl ester obtained above was placed in a thick-wall 25-ml tube with a stirbar, and 1 ml of a 2M solution of ammonia in methyl alcohol was then added. The tube was cooled to -78 °C in a dry-ice bath and further charged with liquid ammonia (~1 ml). The tube, after sealing it with a Teflon stopcock, was heated to 40°C for 12 hours and then cooled to room temperature. The solvent and the excess reagent were removed by slow evaporation under reduced pressure. The off-white solid obtained was purified via reversed-phase HPLC (10-90% CH_3CN/H_2O) to give the desired pyrazinone amide. ^1H NMR ($CDCl_3$): 8.42 (t, J=1.5 Hz, 1H), 8.37 (d, J=8 Hz, 1H), 8.25 (s, 1H), 7.61 (d, J=8 Hz, 1H), 7.58 (d, J= 7.5 Hz, 1H), 7.54 (m, 1H), 7.48-7.40 (m, 3H), 3.70 (s, 3H)

MS: m/e 390 $(M+1)^+$

EXAMPLE 2



Step 1: Preparation of:

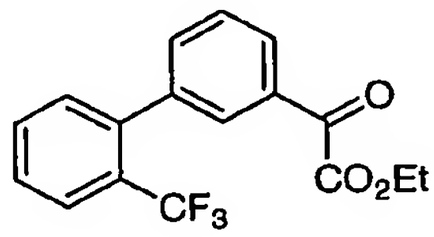


A 25-ml round-bottom flask with a stirbar was charged 1-bromo-3-iodobenzene (1.01 g) and 2-(trifluoromethyl) phenylboronic acid (0.580 g), followed by aq.2M Na_2CO_3 (3 ml), toluene (10 ml) and $Pd(Ph_3P)_4$ (0.139 g). The mixture was heated at 100 °C for 2 hours, then cooled to room temperature, diluted with 30 ml saturated NH_4Cl and extracted with 30 ml hexanes (2 times). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was purified by column chromatography on silica gel (using hexanes) to give the desired biphenyl bromide as an oil.

^1H NMR ($CDCl_3$): 7.80 (d, J=8 Hz, 1H), 7.62 (t, J=7.5 Hz, 1H), 7.58 (m, 1H), 7.55-7.52 (m, 2H), 7.36 (d, J=8 Hz, 1H), 7.32 (m, 2H)

MS (ESI): m/e 301/303 $(M+1)^+$

Step 2: Preparation of:



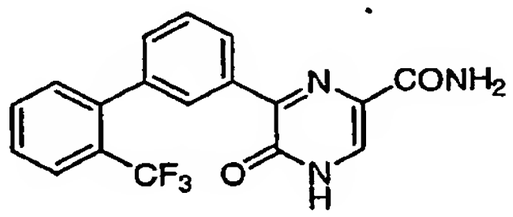
To a solution of the biphenyl bromide from Step 1 above (0.600 g) in anhydrous THF (5 ml) at -78°C was added a 1.6M solution of nBuLi in hexanes (1.42 ml) dropwise in 5 min. The resulting bright yellow solution, after stirring at -78°C for 15 min, was cannulated into another flask containing a pre-cooled (-78°C) solution of diethyl oxalate (0.907 g) in anhydrous THF (5 ml). After stirring for 30 min at -78°C, the reaction was quenched with 30 ml of saturated NH_4Cl, and extracted two times with 20

ml EtOAc/hexanes (1/1). The combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by column chromatography using silica gel (15% EtOAc/hexanes) to give the desired keto ester.

^{1}H NMR ($CDCl_3$): 8.10 (d, J=8 Hz, 1H), 8.09 (s, 1H), 7.81 (d, J=8 Hz, 1H), 7.66-7.60 (m, 4H), 7.36 (d, J=8 Hz, 1H), 4.47 (q, J=7.5 Hz, 2H), 1.42 (t, J= 7.5 Hz, 3H)

MS (ESI): m/e 323 $(M+1)^+$

Step 3: Preparation of



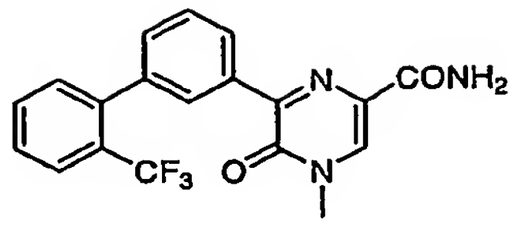
To a solution of the keto ester from Step 2 above (0.410 g) in anhydrous methanol (6 ml) was added methyl-2,3-diamino propionate (0.525 g) at ambient temperature, giving rise to a white suspension. After 15 min of stirring, a solution of NaOMe (2.35 ml, 25% w/w) was added slowly over 5 min. The resulting yellow reaction was stirred at room temperature under air for 30 min before being concentrated under reduced pressure. The solid obtained was treated with 1N HCl (40 ml) and extracted with EtOAc (2X 40 ml). The combined organic phase was dried over sodium sulfate, concentrated and dried *in vacuo*. The crude pyrazinone carboxylic acidthus obtained was carried onto the next reaction described below.

A 50-ml round-bottom flask equipped with a stirbar and septum was charged with the crude acid (from above) and anhydrous DMF (4 ml) under N_2. 1,1'-carbonyl diimidazole (0.437 g) was added, and the mixture was heated at 40°C for 15 min. NH_4OAc (0.406 g) was then introduced in one portion and the mixture was stirred at room temperature overnight. The reaction was diluted with 50 ml saturated NH_4Cl solution, and extracted (2 times) with 50 ml EtOAc. The combined organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purified by column chromatography on silica gel (EtOAc) to give the desired pyrazinone amide.

^{1}H NMR (CD_3OD): 6.91 (d, J=8 Hz, 1H), 6.85 (s, 1H), 6.52 (s, 1H), 6.40 (s, 3H), 6.26 (d, J=8 Hz, 1H), 6.11 (t, J= 8 Hz, 1H), 6.03 (t, J=8 Hz, 1H), 5.97 (t, J=8 Hz, 1H), 5.89 (t, J=8.5 Hz, 1H)

MS: m/e 360 $(M+1)^+$

Step 4: Preparation of:



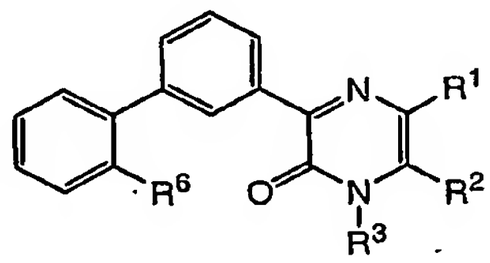
To a solution of the amide (from Step 3) (0.268 g) in diethyl ether (2 ml) and methyl alcohol (2 ml) was added 0.75 ml of 2M solution of $TMSCHN_2$ in hexanes at 0 °C. The resulting yellow mixture was stirred at 0 °C for 1 hour and concentrated *in vacuo*. The crude product was purified by reversed-phase HPLC (10-90% CH_3CN/H_2O) to give the desired N-methylated product.

^1H NMR ($CDCl_3$): 8.34 (d, J=7.5 Hz, 1H), 8.24 (s, 1H), 8.19 (s, 1H), 7.75 (d, J=8 Hz, 1H), 7.58 (t, J=7.5 Hz, 1H), 7.51-7.47 (m, 2H), 7.44 (d, J= 7.5 Hz, 1H), 7.38 (d, J=8 Hz, 1H), 7.29 (s, 1H)

MS (ESI): m/e 374 $(M+1)^+$.

Other Examples of the instant invention are provided below.

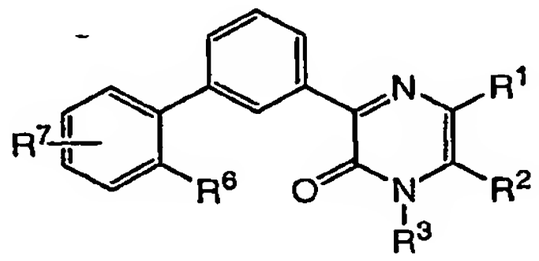
TABLE 1



Example #	R^6	R^3	R^2	R^1	(m/e) (M+H)
3	$-OCF_3$	H	H	$-CONH_2$	376
4	$-OCF_3$	CH_3	H	-COOH	377
5	$-OCF_3$	CH_3	$-CONH_2$	H	390
6	$-CF_3$	CH_3	$-CONH_2$	H	374
7	$-CF_3$	H	H	-COO-t-Bu	417
8	$-CF_3$	H	H	-CONH-t-Bu	416
9	$-CF_3$	H	H	-COOH	361
10	$-OCH_2CF_2CF_3$	H	H	$-CONH_2$	440

Example #	R^6	R^3	R^2	R^1	(m/e) (M+H)
11	$-OCH_2CF_2CF_3$	H	H	-COOH	441
12	$-OCH_2CF_3$	H	H	$-CONH_2$	390
13	$-OCH_2CF_3$	CH_3	H	$-CONH_2$	404
14	$-OCH_2CF_3$	H	$-CONH_2$	H	390
15	$-OCH_2CF_3$	CH_3	$-CONH_2$	H	404
16	$-OCH_2CF_2CF_3$	CH_3	H	$-CONH_2$	454
17	$-OCH_2CF_3$	H	H	-COOH	391
18	$-CF_3$	$-CH_2CF_3$	H	$-CONH_2$	442
19	$-CF_3$	$-C(CH_3)_3$	H	$-CONH_2$	416
20	$-CF_3$	$-CH(CH_3)_2$	H	$-CONH_2$	402
21	$-CF_3$	$-CH_2CH_3$	H	$-CONH_2$	388
22	$-OCF_3$	CH_3	$-CONH_2$	$-CONH_2$	432

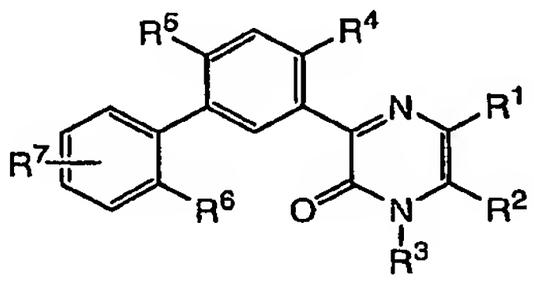
TABLE 2



Example #	R^7	R^6	R^3	R^2	R^1	(m/e) (M+H)
23	4-CF_3	$-CF_3$	$-CH_3$	H	$-CONH_2$	442
24	4-CF_3	$-CF_3$	$-CH_3$	$-CONH_2$	H	442
25	5-F	$-OCF_3$	$-CH_3$	H	$-CONH_2$	408
26	5-CF_3	$-OCF_3$	$-CH_3$	H	$-CONH_2$	458
27	5-F	$-OCF_3$	H	H	$-CONH_2$	394
28	5-F	$-OCH_2CF_2CF_3$	H	H	$-CONH_2$	458
29	5-F	$-OCH_2CF_3$	H	H	$-CONH_2$	408
30	5-F	$-OCH_2CF_2CF_3$	$-CH_3$	H	$-CONH_2$	472
31	5-F	$-OCH_2CF_3$	$-CH_3$	H	$-CONH_2$	422
32	6-F	$-CF_3$	H	H	$-CONH_2$	378

Example #	R^7	R^6	R^3	R^2	R^1	(m/e) (M+H)
33	3-F	$-CF_3$	H	H	$-CONH_2$	378
34	6-F	$-CF_3$	$-CH_3$	H	$-CONH_2$	392
35	3-F	$-CF_3$	$-CH_3$	H	$-CONH_2$	392
36	5-F	$-CF_3$	$-CH_3$	H	$-CONH_2$	392
37	4-F	$-CF_3$	$-CH_3$	H	$-CONH_2$	392
38	4-F	$-CF_3$	H	H	$-CONH_2$	378
39	5-F	$-CF_3$	H	H	$-CONH_2$	378
40	5-CH_3	$-CF_3$	$-CH_3$	H	$-CONH_2$	388
41	4-CH_3	$-CF_3$	$-CH_3$	H	$-CONH_2$	388

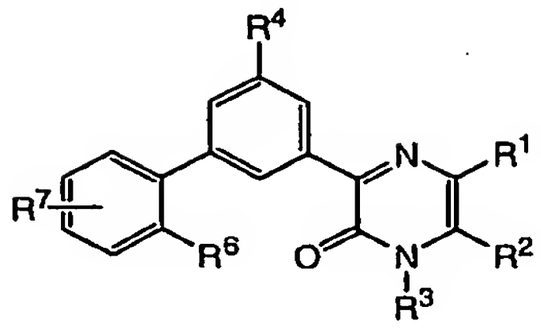
TABLE 3



Example #	R^7	R^6	R^5	R^4	R^3	R^2	R^1	(m/e) (M+H)
42	H	$-OCF_3$	F	H	$-CH_3$	$-CONH_2$	H	408
43	H	$-OCF_3$	F	H	$-CH_3$	H	$-CONH_2$	408
44	H	$-OCF_3$	H	F	$-CH_3$	H	H	365
45	H	$-OCF_3$	H	F	$-CH_3$	H	$-CONH_2$	408
46	H	$-OCH_2CF_3$	H	F	$-CH_3$	H	$-CONH_2$	422
47	H	$-OCF_3$	H	F	$-CH_3$	H	-COOH	409
48	5-F	$-OCF_3$	F	H	$-CH_3$	H	$-CONH_2$	426
49	5-F	$-OCF_3$	H	F	$-CH_3$	H	$-CONH_2$	426
50	H	$-CF_3$	H	F	$-CH_3$	H	$-CONH_2$	392
51	H	$-CF_3$	F	H	$-CH_3$	H	$-CONH_2$	392
52	H	$-OCF_3$	H	F	H	H	$-CONH_2$	394
53	H	$-OCF_3$	F	H	H	H	$-CONH_2$	394

Example #	R^7	R^6	R^5	R^4	R^3	R^2	R^1	(m/e) (M+H)
54	5-F	$-OCF_3$	F	H	H	H	$-CONH_2$	412
55	H	$-CF_3$	F	H	$-CH_3$	H	-COOH	393
56	5-F	$-OCH_2CF_2CF_3$	F	H	$-CH_3$	H	$-CONH_2$	490
57	H	$-CF_3$	H	F	$-CH_3$	H	-COOH	393
58	H	$-OCF_3$	F	H	$-CH_3$	H	$-COOCH_3$	423
59	H	$-CF_3$	F	H	$-CH_3$	H	$-COOCH_3$	407
60	H	$-CF_3$	F	H	$-CH_3$	H	$-COOCH_3$	353
61	5-F	$-OCH_2CH_3$	F	H	$-CH_3$	H	$-COOCH_3$	401
62	5-F	$-OCH_2CF_3$	F	H	$-CH_3$	H	$-COOCH_3$	455
63	H	$-OCF_3$	F	H	H	H	-COOH	395
64	H	$-OCF_3$	H	F	H	H	-COOH	395
65	5-F	$-OCH_2CF_2CF_3$	F	H	$-CH_3$	H	-COOH	491
66	H	$-CF_3$	H	F	H	H	$-CONH_2$	378
67	H	$-CF_3$	Br	H	$-CH_3$	H	$-COOCH_3$	453
68	H	$-CF_3$	F	H	H	H	$-CONH_2$	378
69	H	$-CF_3$	Br	H	$-CH_3$	H	$-CONH_2$	452
70	5-F	$-CF_3$	H	F	$-CH_3$	H	$-CONH_2$	410
71	H	$-CF_3$	Br	H	H	H	$-COOCH_3$	439
72	H	$-CF_3$	Br	H	H	H	-COOH	425
73	5-F	$-OCH_2CF_3$	F	H	H	H	$-CONH_2$	426
74	3-F	$-CF_3$	F	H	$-CH_3$	H	$-CONH_2$	410
75	3-F	$-CF_3$	H	F	$-CH_3$	H	$-CONH_2$	410
76	5-F	$-CF_3$	F	H	$-CH_3$	H	$-CONH_2$	410
77	4-F	$-CF_3$	F	H	$-CH_3$	H	$-CONH_2$	410
78	4-F	$-CF_3$	H	F	H	H	$-CONH_2$	396

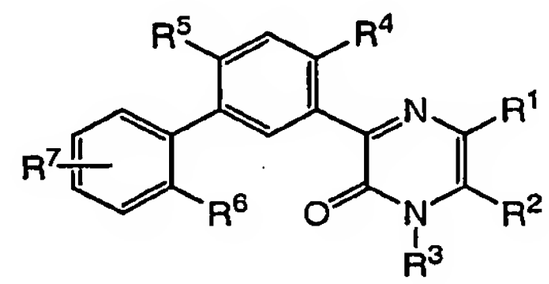
TABLE 4



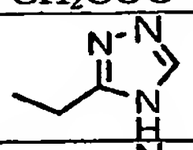
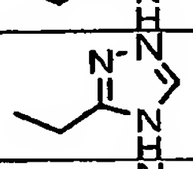
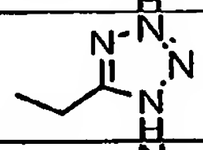
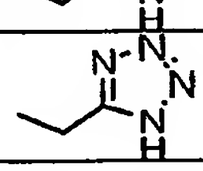
Example #	R^7	R^6	R^4	R^3	R^2	R^1	(m/e) (M+H)
79	H	$-OCF_3$	F	$-CH_3$	H	$-CONH_2$	408
80	H	$-OCF_3$	F	$-CH_3$	$-CONH_2$	H	408
81	H	$-OCF_3$	F	$-CH_3$	H	-COOH	409
82	H	$-OCF_3$	F	H	H	$-CONH_2$	394
83	H	$-OCF_3$	F	H	H	-COOH	395
84	H	$-CF_3$	F	$-CH_3$	H	$-CONH_2$	392
85	H	$-CF_3$	F	$-CH_3$	H	-COOH	393
86	5-F	$-OCH_2CF_2CF_3$	F	$-CH_3$	H	$-CONH_2$	490
87	5-F	$-OCH_2CF_3$	F	$-CH_3$	H	$-CONH_2$	440
88	H	$-OCF_3$	F	$-CH_3$	H	-COOCH3	423
89	5-F	$-CF_3$	F	$-CH_3$	H	$-CONH_2$	410
90	H	$-CF_3$	F	H	H	$-CONH_2$	378
91	3-F	$-CF_3$	F	$-CH_3$	H	$-CONH_2$	410

5

TABLE 5

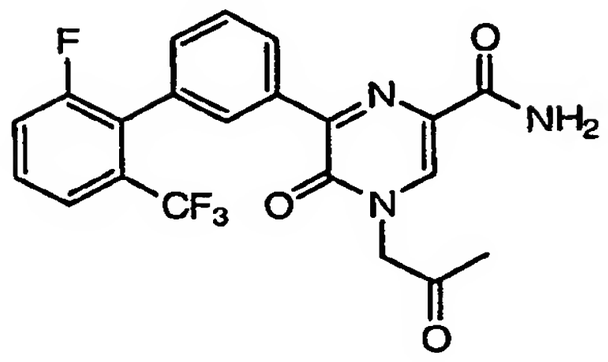


Example #	R^7	R^6	R^5	R^4	R^3	R^2	R^1	(m/e) (M+H)
92	H	OCF_3	H	H	CH_2CONH_2	H	$CONH_2$	433

Example #	R^7	R^6	R^5	R^4	R^3	R^2	R^1	(m/e) (M+H)
93	H	CF_3	H	H	CH_2CONH_2	H	$CONH_2$	417
94	H	OCF_3	H	H	CH_2COOH	H	$CONH_2$	434
95	H	OCF_3	H	H	CH_2COO-tBu	H	$CONH_2$	489
96	H	OCF_3	H	H	CH_2CN	H	$CONH_2$	415
97	H	CF_3	H	H	CH_2CN	H	$CONH_2$	399
98	H	CF_3	H	H	CH_2COOH	H	$CONH_2$	418
99	H	CF_3	H	H	CH_2COO-tBu	H	$CONH_2$	474
100	H	OCF_3	H	H		H	$CONH_2$	457
101	H	CF_3	H	H		H	$CONH_2$	441
102	H	CF_3	H	H		H	$CONH_2$	442
103	H	OCF_3	H	H		H	$CONH_2$	458
104	H	OCF_3	H	H	CH_2CH_2OH	H	$CONH_2$	420
105	H	CF_3	H	H	CH_2CH_2OH	H	$CONH_2$	404
106	H	OCF_3	H	H	$CH_2CH_2NH_2$	H	$CONH_2$	419
107	H	CF_3	H	H	$CH_2CH_2NH_2$	H	$CONH_2$	403
108	H	OCF_3	H	H	$CH_2CH_2N(CH_3)_2$	H	$CONH_2$	447
109	H	CF_3	H	H	$CH_2CH_2N(CH_3)_2$	H	$CONH_2$	431
110	4-F	CF_3	H	H	CH_2CONH_2	H	$CONH_2$	451
111	5-F	CF_3	H	H	CH_2CONH_2	H	$CONH_2$	451
112	H	CF_3	F	H	CH_2CONH_2	H	$CONH_2$	451
113	H	CF_3	F	H	CH_2CONH_2	H	$CONH_2$	451
114	4-F	CF_3	F	H	CH_2CONH_2	H	$CONH_2$	469
115	5-F	CF_3	F	H	CH_2CONH_2	H	$CONH_2$	469

5

EXAMPLE 116

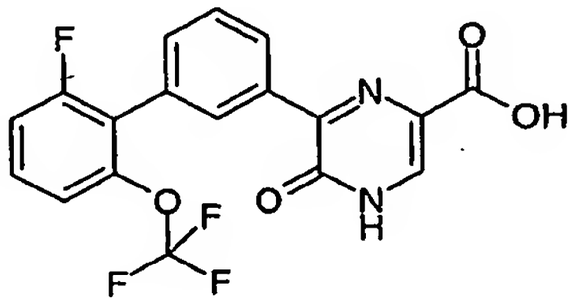


To a solution of the amide (Example 32) (0.060 g) in DMF (1 mL), was added chloroacetone (0.029 g) and potassium carbonate (0.043 g). The resulting mixture was stirred at 40°C for 40 minutes, and then diluted with 10 mL saturated NH_4Cl solution and extracted twice with 20 mL EtOAc/hexanes (1/1). The combined organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purifed to give the desired methyl ketone.

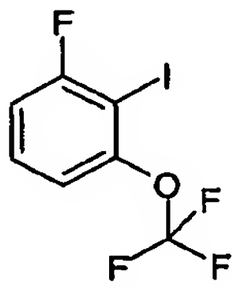
^{1}H NMR (CD_3OD): 8.47 (m, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 7.67 (m, 1H), 7.63 (m, 1H), 7.50 (m, 1H), 7.41 (m, 1H), 5.13 (s, 2H), 2.15 (s, 3H).

MS: m/e 434 $(M+1)^+$.

EXAMPLE 117



Step 1: Preparation of



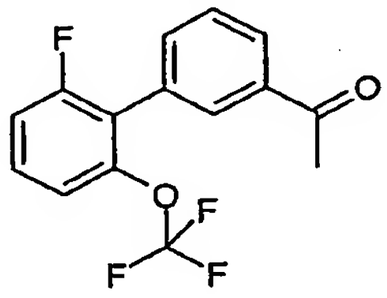
To the solution of 3-(trifluoromethoxyl) fluorobenzene (1g, 5.5 mmol) in 10mL THF at -78^{0}C, n-BuLi (1.6M, 3.75mL) was added dropwise. The resulting solution was stirred at

-78^{0}C for 30 min. I_2 (2.1g, 8.25 mmol) in THF (5mL) was added. The mixture was warmed to room temperature and then quenched with Na_2CO_3 in saturated $Na_2S_2O_3$ (1:10) (30mL). The crude product was extracted with ether. The ether layer was dried over Na_2SO_4 and filtered through a short silica gel column to give the desired iodide as an oil.

^{1}H NMR ($CDCl_3$): 7.39 (m, 1H), 7.12 (d, J=9.0 Hz, 1H), 7.05 (t, J=6.0 Hz, 1H)

MS (ESI): m/e 307 $(M+1)^+$

Step 2: Preparation of

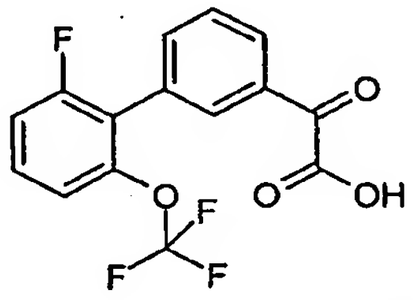


To a solution of the aryl iodide (1.4g) (from Step 1 above) in anhydrous dioxane (20 mL) were added 3-acetylphenylboronic acid (2.5g) and KF (0.87g) followed by $Pd(dppf)_2Cl_2$ (376mg). The mixture was heated to 90^{0}C for 2 h. After cooling to room temperature, the mixture was filtered through a pad of celite, washed with EtOAc. The filtrate was concentrated *in vacuo*, and the crude product, thus obtained, was purified by column chromatography on silica gel using 10% ether in hexane to give the desired product as an oil.

^{1}H NMR ($CDCl_3$): 8.05 (m, J=8 Hz, 1H), 8.02 (s, 1H), 7.61 (s, 1H), 7.60 (s, 1H), 7.42 (m, 1H), 7.22 (d, J=12Hz, 1H), 7.20 (m, 1H)

MS (ESI): m/e 299 $(M+1)^+$

Step 3: Preparation of



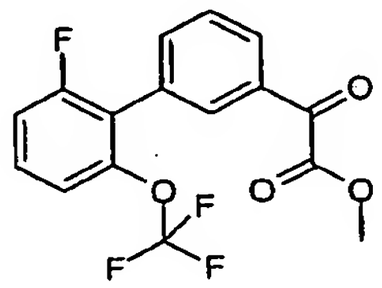
To a solution of biphenyl acetophenone (2.8g) (from last Step 2) in dry pyridine (40mL), Selenium dioxide (2.1g) was added, and the mixture was heated at 100^{0}C for 2 h. The precipitated Selenium (black) was filtered off, and the filterate was concentrated under reduced pressure. The residue obtained was treated with 10% NaOH and extracted with ether. The

aqueous layer was acidified and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to give desired product as a solid.

^{1}H NMR ($CDCl_3$): 8.46 (d, J=8Hz, 1H), 8.41 (s, 1H), 7.75 (d, J=8Hz, 1H), 7.67 (t, J=15 Hz, 1 H), 7.45 (m, 1H), 7.25 (d, J=7 Hz, 1H), 7.21 (t, J=18 Hz, 1H).

MS (ESI): m/e 329 $(M+1)^+$

Step 4: Preparation of

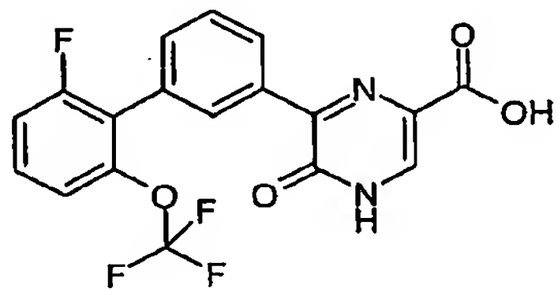


To a solution of the keto-acid (2g) (from Step 3) in DMF (50 mL) were added dimethyl sulfate (1.5g) and K_2CO_3 (3.3g). The mixture was stirred at 50^{0}C for 2 h. The solvent was removed under reduced pressure, and the residue obtained was dissolved in EtOAc, washed with 1N HCl, dried over Na_2SO_4 and purified by column chromatography on silica gel.

^{1}H NMR ($CDCl_3$): 8.12 (d, J=8Hz, 1H), 8.09 (s, 1H), 7.72 (d, J=9Hz, 1H), 7.63 (t, J=15 Hz, 1 H), 7.45 (m, 1H), 7.24 (d, J=7 Hz, 1H), 7.19 (t, J=18 Hz, 1H)

MS (ESI): m/e 343 $(M+1)^+$

Step 5: Preparation of



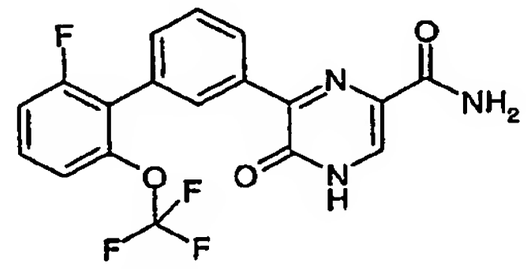
To a solution of the keto-ester (1.5g) (from Step 4) in MeOH (10 mL) was added methyl-2,3-diamino propionate (1.2g) followed by 40% NaOMe (5.7mL). The mixture was stirred at room temperature for 2 h, then acidified with concentrated. After stirring at room temperature overnight, the solvent was removed under reduced pressure. The residue obtained was then dissolved in 10% KOH, washed with ether and acidified with HCl. The mixture was

extracted with EtOAc to give the crude product which was purified by reversed-phase chromatography to give 1.2g of the final pyrazinone carboxylic acid.

^{1}H NMR (CD_3OD): 8.49 (d, J=9Hz, 1H), 8.46 (s, 1H), 8.07(s, 1H), 7.59 (t, J=16 Hz, 1 H), 7.47-7.54 (m, 2H), 7.26-7.32 (m, 2H).

MS (ESI): m/e 395 $(M+1)^+$

EXAMPLE 118

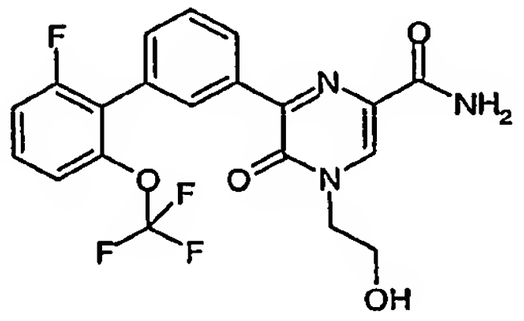


To a solution of the pyrazinone carboxylic acid (1.2g) (from Step 5 of Example 117) in anhydrous DMF (10 mL) was added 1,1'-carbonyl diimidazole (1.4g). The mixture was heated at 40^{0}C for 15min, and anhydrous NH_4OAc (1.5g) was then introduced in one portion to the reaction. The mixture was stirred at room temperature overnight, then diluted with saturated NH_4Cl solution (50 mL), and extracted (2 X) with EtOAc. The combined organic phase was dried over Na_2SO_4, concentrated *in vacuo*, and purified by reversed-phase chromatography.

^{1}H NMR (CD_3OD): 8.49 (d, J=9Hz, 1H), 8.46 (s, 1H), 8.07(s, 1H), 7.59 (t, J=16 Hz, 1 H), 7.47-7.54 (m, 2H), 7.26-7.32 (m, 2H).

MS (ESI): m/e 394 $(M+1)^+$

EXAMPLE 119



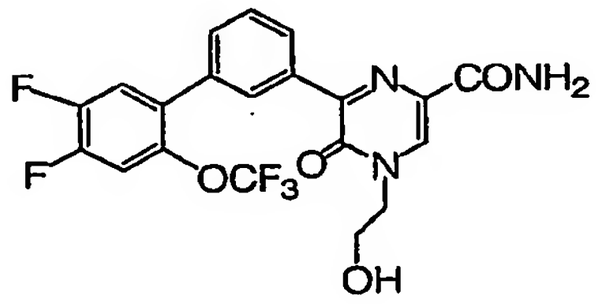
To a solution of the amide (100 mg) (from Example 118) in dry DMF (2 mL) were added , K_2CO_3 (36 mg) and 2-iodoethanol (90 mg). The reaction mixture was heated at 50 °C for 2 h,

then cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in EtOAc, washed with 1N HCl, dried over Na_2SO_4 and concentrated *in vacu*. The crude product obtained was purified by column chromatography using silica gel (1:2 acetone to ethyl acetate) to give the desired product as white solid.

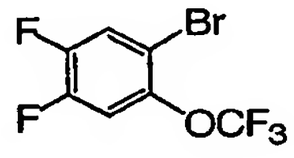
^{1}H NMR (CD_3OD): 8.46 (d, J=8Hz, 1H), 8.42 (s, 1H), 8.31 (s, 1H), 7.50 (t, J=16 Hz, 1 H), 7.48-7.58 (m, 2H), 7.27-7.34 (m, 2H).

MS (ESI): m/e 438 $(M+1)^+$

EXAMPLE 120



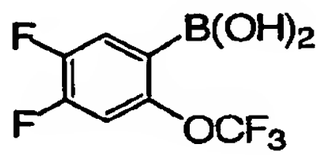
Step 1: Preparation of 3,4-difluoro-6-(trifluoromethoxyl)benzyl bromide



To a cold (0°C) solution of 2-bromo-4,5-difluorophenol (5g, 24mmol) and N-methyl morpholine (5.3mL, 48mmol) in dry THF (20mL) was added phenyl chlorodithioformate (3.4mL, 24mmol). The resulting solution was stirred at room temperature for one hour. After removal of the solvent, the residue was dissolved in ether and washed with water and brine. The ether layer was then dried over anhydrous sodium sulfate. After concentration, the crude product was purified via column chromatography on silica gel to afford the thiocarbonate as a white solid, 8.5g, 99% yield. This thiocarbonate was then dissolved in dichloromethane in a plastic bottle. At -78°C, HF-pyridine was added, followed by small portions of dibromohydentoin. The reaction mixture was allowed to warm up to room temperature over 2 hours. After another 2 hours stirring at room temperature, the reaction was quenched with 2N NaOH aqueous and extracted with ether. The organic layer was separated and washed with water and brine. The

ether layer was then dried over anhydrous sodium sulfate. After concentration, the crude product was applied to column chromatography on silica gel to afford the final product as colorless oil, 6.0g, 92% yield. This product was used in Step 2 below.

Step 2: Preparation of 3,4-difluoro-6-trifluoromethoxyl)benzyl boronic acid

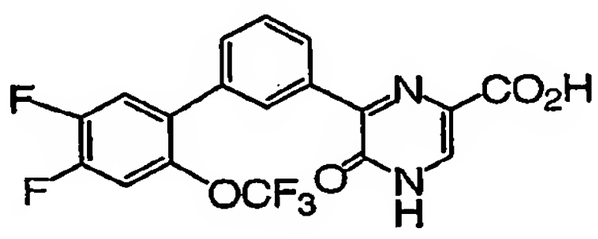


To the solution of 3,4-difluoro-6-(trifluoromethoxyl)phenyl bromide (2g, 7.2mmol) in dry THF (20mL) was added isopropylmagnesiumchloride (5.4mL, 2M in THF, 11mmol). The reaction mixture was stirred at room temperature for 6 hours before it was quenched with triisopropyl borate (2g, 11mmol). The resulting mixture was stirred at room temperature for 14 hours. Finally this reaction was treated with 2N HCl and was stirred for 3 hours. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. After concentration, the crude product was dissolved in 2N NaOH and washed with ether (once). The aqueous layer was then acidified to pH ~1 and extracted with ethyl acetate. After concentration, the product was collected as an off-white solid.

^{1}H NMR ($CDCl_3$) (δ, ppm): 7.76 (t, J=19 Hz, 1H), 7.15 (dd, J=12, 19 Hz, 1H), 5.08 (bs, 2H).

MS (ESI): m/e 243 $(M+1)^+$

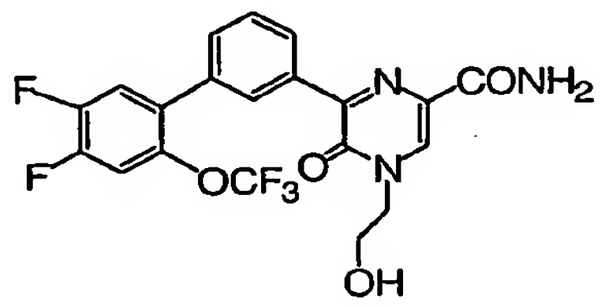
Step 3: Preparation of



To the solution of 3,4-difluoro-6-(trifluoromethoxyl)benzyl boronic acid (from Step 2 above) (263mg, 1.1mmol), 1-(3'-bromobenzene)-3-carboxylpyrazinone (from Step 1, Example 250) (200mg, 0.68mmol), and Na_2CO_3 (2N, 4mL) in ethanol (4ml), under N_2, was added $Pd(dppf)Cl_2$ (56mg, 0.01mmol). The resulting yellow suspension was stirred at 90°C for 6 hours. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was partitioned between ethyl acetate and 2N HCl. The aqueous layer was extracted with ethyl

acetate. The combined organic layer was washed with brine and dried over anhydrous sodium sulfate. After concentration, the product was dried on a high vacuum pump and used in Step 4.

Step 4: Preparation of

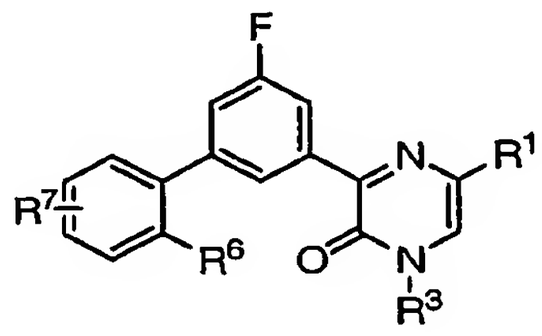


The crude acid from Step 3 above was dissolved in dry DMF and treated with carbonyldiimidazole (165mg, 1.0mmol). The reaction was stirred at 55°C for 2 hours before the addition of ammonium acetate (250mg, excess). After stirring at room temperature for overnight, the reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride aqueous and brine. After concentration, the crude product was dried on vacuum pump. The crude pyrazinone amide (50mg, 0.11mmol) was dissolved in dry DMF (1ml) and was treated with 1-iodoethanol (29mg, 0.18mmol) and potassium carbonate (24mg, 0.18mmol). The reaction mixture was stirred at room temperature for 1 hour. The mixture was diluted with ethyl acetate and washed with water and brine. After concentration, the final product was purified via column chromatography on silica gel, as a yellow solid.

^{1}H NMR ($CDCl_3$) (δ, ppm): 8.35 (m, 2H), 7.53 (m, 3H); 7.46 (bs, 1H,), 7.37 (t, J=17 Hz, 1H), 4.27 (d, J=6 Hz, 2H), 4.08 (d, J=6 Hz, 2H).

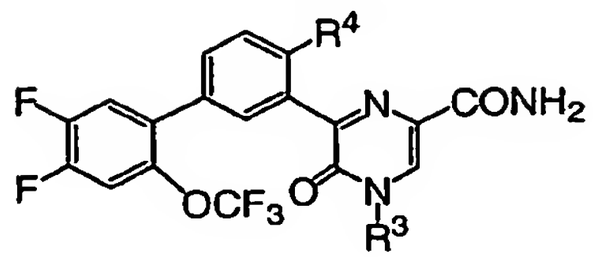
MS (ESI): m/e 456 $(M+1)^+$

TABLE 6



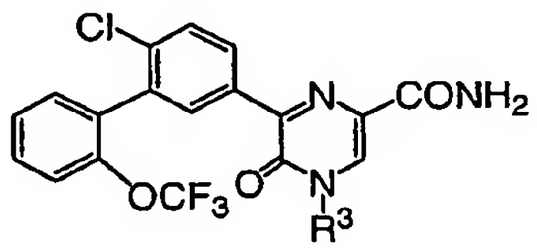
Example #	R^7	R^6	R^3	R^1	(m/e) (M+H)
121	4-F	$-CF_3$	$-CH_3$	$-CONH_2$	410
122	5-F	$-CF_3$	H	$-CONH_2$	396
123	H	CF_3	$-CH_2CH_2OH$	$-CONH_2$	422
124	H	$-CF_3$	$-CH_2CH_2F$	$-CONH_2$	424
125	H	$-OCF_3$	$-CH_2CH_2OH$	$-CONH_2$	438
126	H	$-OCF_3$	$-CH_2CH_2CH_2OH$	$-CONH_2$	452
127	H	$-OCF_3$	$-CH_2CONH_2$	$-CONH_2$	451
128	H	$-OCF_3$	$-CH(CH_3)CONH_2$	$-CONH_2$	465
129	H	$-OCF_3$	$-CH_2CH_3$	$-CONH_2$	422
130	H	$-OCF_3$	$-CH_2CH_2F$	$-CONH_2$	440
131	H	$-CF_3$	$-CH_2CONH_2$	$-CONH_2$	435
132	H	$-OCF_3$	$-CH_2SO_2NH_2$	$-CONH_2$	487
133	3-F	$-CF_3$	$-CH_2SO_2NH_2$	$-CONH_2$	471
134	H	$-CF_3$	$-CH_2CH_3$	$-CONH_2$	406
135	H	$-CF_3$	$-CH_2CH_2CH_2OH$	$-CONH_2$	436
136	H	$-OCF_3$	$-CH_2CH_2Cl$	$-CONH_2$	456
137	H	$-OCF_3$	$-CH_2CH_2N_3$	$-CONH_2$	463
138	H	$-OCF_3$	$-CH_2CH_2NH_2$	$-CONH_2$	437
139	H	$-CF_3$	$-CH(CH_3)CONH_2$	$-CONH_2$	449
140	H	$-OCF_3$	$-CH_2CONHCH_3$	$-CONH_2$	464
141	4-F	$-CF_3$	$-CH_2CONH_2$	$-CONH_2$	453
142	4-F	$-CF_3$	$-CH_2CH_2OH$	$-CONH_2$	440
143	4-F	$-CF_3$	$-CH_2CH_3$	$-CONH_2$	424
144	4-F	$-CF_3$	H	$-CONH_2$	394
145	5-F	$-CF_3$	$-CH_2CH_2OH$	$-CONH_2$	440
146	5-F	$-CF_3$	$-CH_2CONH_2$	$-CONH_2$	453
147	H	$-OCF_3$	$-CH_2C(=O)CH_3$	$-CONH_2$	450

TABLE 7



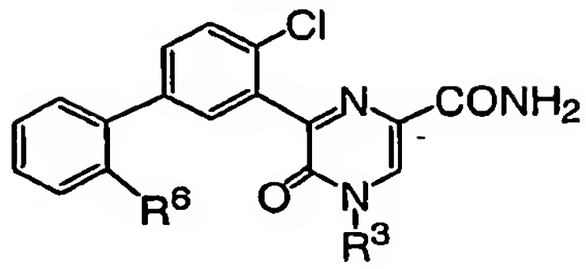
Example #	R^4	R^3	MS Data (m/e, M+1)
148	F	H	430
149	F	CH_2CONH_2	487
150	F	CH_2CH_2OH	474
151	F	CH_3	444
152	H	H	412
153	H	CH_2CONH_2	468
155	H	CH_3	426

TABLE 8



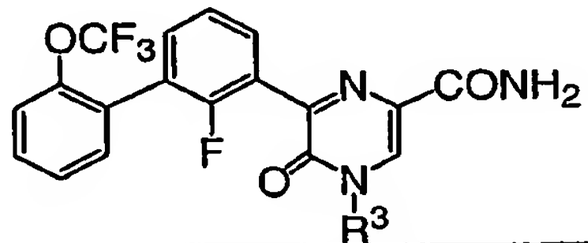
Example #	R^3	MS Data (m/e, M+1)
156	CH_2CONH_2	467
157	CH_2CH_2OH	454

TABLE 9



Example #	R^6	R^3	MS Data(m/e, M+1)
158	OCF3	CH_2CONH_2	467
159	OCF3	$CH(CH_3)CONH_2$	481
160	OCF3	CH_2CH_2OH	454
161	OCF3	$CH_2CH_2CH_2OH$	468
162	OCF3	CH_2CH_3	438
163	CF3	CH_2CONH_2	451
164	CF3	$CH(CH_3)CONH_2$	465
165	CF3	CH_2CH_2OH	438
166	CF3	$CH_2CH_2CH_2OH$	452
167	CF3	CH_2CH_3	422

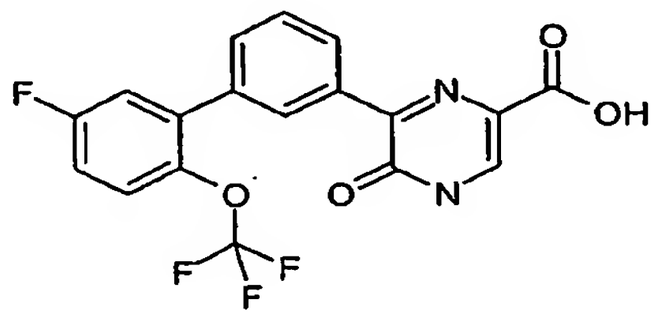
TABLE 10



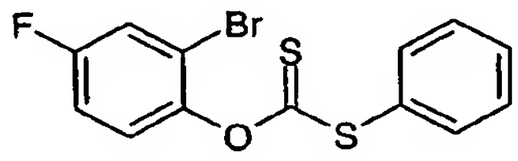
Example #	R^3	MS Data (m/e, M+1)
168	H	394
169	CH_2CONH_2	451
170	CH_2CH_2OH	438
171	$CH(CH_3)CONH_2$	465
172	$CH_2CH_2CH_2OH$	452
173	CH_2CH_3	422
174	$CH_2CONHCH_3$	465

Example #	R^3	MS Data (m/e, M+1)
175	$CH_2CON(CH_3)_2$	479
176	$CH_2CO_2CH_3$	466

EXAMPLE 177

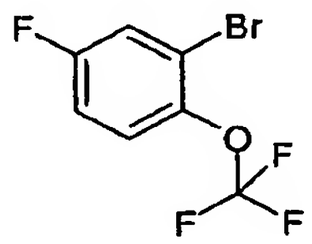


Step 1: Preparation of



To a solution of 2-bromo-4-fluorophenol (5g) in THF (100 mL) at 0°C were added N-methylmorpholine (5.25g) and Phenyl chlorodithioformate (5.18g). The reaction mixture was stirred at 0°C for 2 h and then diluted with EtOAc (100 mL), washed with water (100mL)(2X) and then brine (100 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the desired xanthate as a yellow solid.
^{1}H NMR ($CDCl_3$): 7.65 (m, 2H), 7.51 (m, 2H), 7.38 (m, 1H), 7.08-7.16 (m, 3H).
MS (ESI): m/e 344 $(M+1)^+$

Step 2: Preparation of

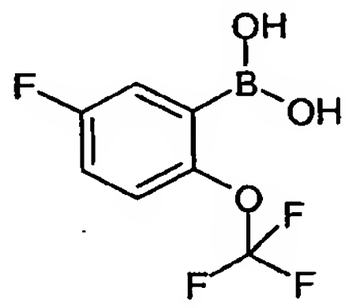


A solution of the xanthate (1g) (from Step 1 above) in CH_2Cl_2 (10 mL) was added to HF/pyridine (4.4M, 4mL) placed in a 250ml plastic bottle. The bottle was cooled to -78°C and 1,3-dibromo-5,5-dimethyl hydantoin (5.1g) was added in portion while stirring. The reaction mixture was allowed to warm up to room temperature; the progress of the reaction was monitored by NMR. The reaction mixture was carefully neutralized by pouring into a mixture of 15g NaOH/ 100g ice. The resulting mixture was filtered through a pad of celite and washed with ether. The filtrate was separated, the organic layer was washed with 10% KOH and 1N HCl, dried over Na_2SO_4, purified by column chromatography on silica gel (using hexane) to give the desired aryl bromide as a colorless oil.

^{1}H NMR ($CDCl_3$): 7.42 (m, 1H), 7.33 (m, 1H), 7.38 (m, 1H), 7.09 (m, 1H).

MS (ESI): m/e 192 $(M+1)^+$

Step 3: Preparation of

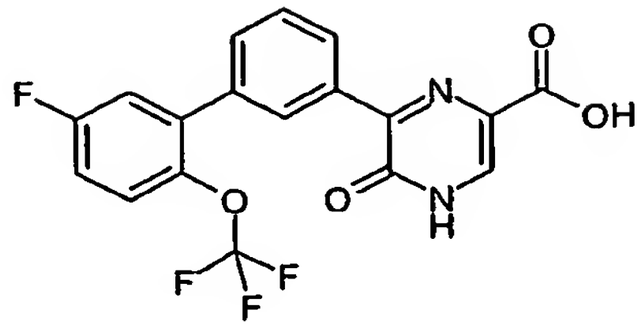


To a solution of the aryl bromide (from Step 2 above) (5g) in THF (25 mL) was added Isopropylmagnesium chloride (15 mL, 2.0M in THF) at room temperature. After stirring at the ambient for 2 h, $B(OiPr)_3$ was added to the reaction and stirred overnight. The reaction was quenched with 1N HCl, stirred at room temperature for 30min and extracted with EtOAc. The residue obtained after removal of the solvent *in vacuo,* was dissolved in 10% KOH, extracted with ether. The aqueous phase was acidified with concentrated HCl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to give the aryl boronic acid as a white solid.

^{1}H NMR ($CDCl_3$): 7.28-7.32 (m, 1H), 7.17-7.22 (m, 2H)

MS (ESI): m/e 225 $(M+1)^+$

Step 4: Preparation of:

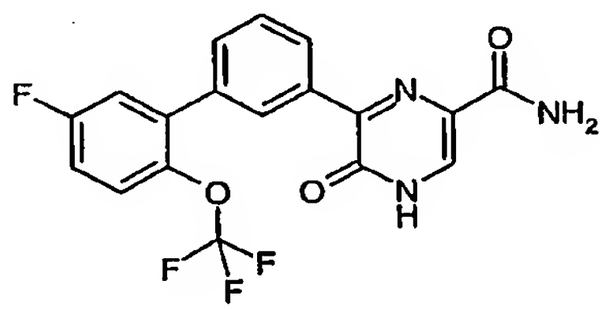


To a 250 ml Schlenk flask equipped with a stirring bar was charged with 1.0 g of boronic acid (from Step 3 above) and 1.0 g of 3-bromo-phenyl pyrazinone carboxylic acid (from Step 2 of Example 1), followed by 15 ml EtOH and 20 ml 1M Na_2CO_3. After reaction mixture was flushed with N_2, Pd(dppf)Cl2 (69 mg) was then added. Reaction mixture was heated at 95 °C for 1 hour and then at 80 °C overnight. After reaction mixture was cooled to room temperature, volatiles were removed under vacuum. To the residue was added 80 ml 2 % KOH. Resulting mixture was filtered through a pad of celite to remove highly colored palladium residue. Filtrate was acidified with 3N HCl and extracted with 75 ml EtOAc (2 times). Organics were dried over Na2SO4, filtered and concentrated to give 1.2 g crude product. This material was further purified by recrystallization from mixed solvent of CH_3CN and H_2O to give 0.71 g pale brown solid as the first crop material.

MS (ESI): m/e 395 $(M+1)^+$

EXAMPLE 178

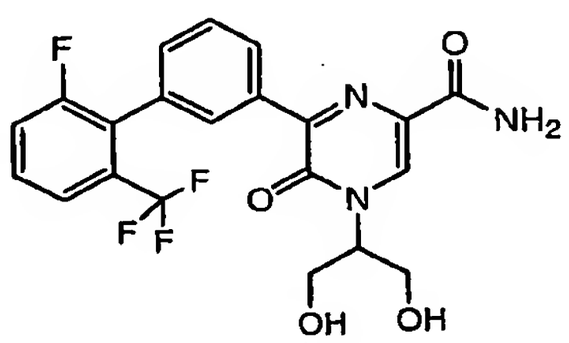
Preparation of:



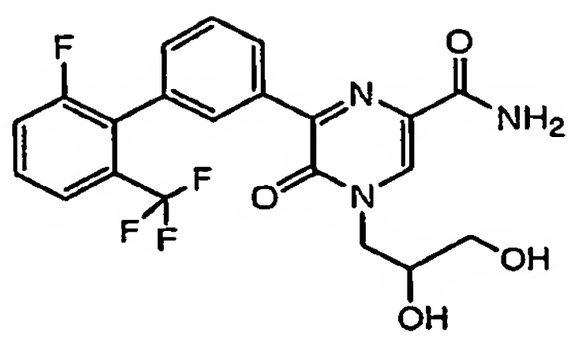
To a solution of the carboxylic acid (from Step 4, Example 177) (0.707 g) in anhydrous DMF (5 mL) was added 1,1'-carbonyldiimidazole (0.5 g). The resulting reaction mixture was stirred at room temperature for 10 minutes and at 50 °C for 15 more minutes. After cooling to room temperature, NH_4OAc (1.0 g) was added as a solid. After stirring at room temperature over night, reaction mixture was diluted with water (100 mL). The precipitate formed was filtered, washed

with water (100 mL) and air dried. The final product product was isolated as pale yellow solid (0.67 g).
MS (ESI): m/e 394 $(M+1)^+$

EXAMPLE 179 and 180



179

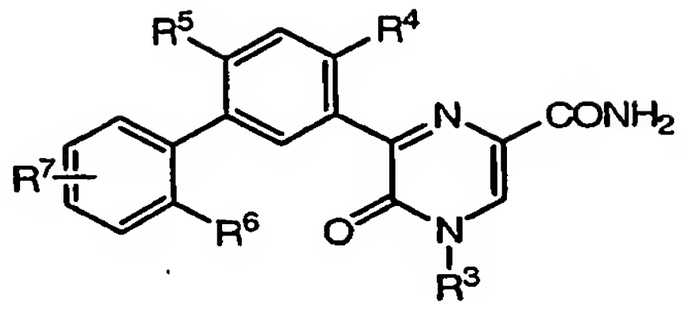


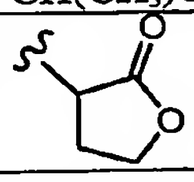
180

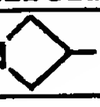
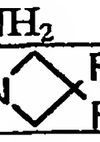
To a mixture of the pyrazinone (Example 32) (0.1 g), K_2CO_3 (36 mg) in DMF (1 mL) was treated with a solution of 2-p-toluenesulfonato-1,3-propane diol (prepared according to the procedure described by Kurimura, M.; Achiwa, K.; *Chem Pharm Bull*, Jap. **1993**, 41, 627-629) (196 mg) in DMF (3 mL) was added to the reaction mixture via a syringe pump over 2 h while the reaction mixture was heated at 90 °C. After heating at 90 °C for an additional 2 h, the reaction was cooled to room temperature and water (1.5 mL) H_2O and 5 drops of TFA were added. The resulting solution was injected into a reversed-phase HPLC column and purified by Gilson HPLC (10-90% CH_3CN/H_2O) to give 52 mg sticky material. This material was further purified on prep-TLC plate by eluting with 3:2 acetone/ethylacetate to give **179** (22 mg) and **180** (10.5 mg) as white solids.

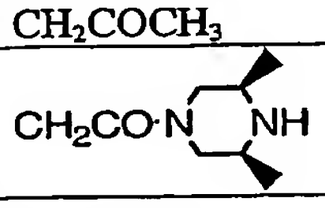
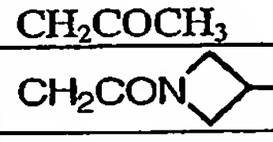
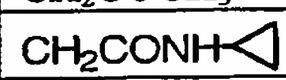
Example 179: MS (ESI): m/e 376 $(M+1)^+$
^{1}H NMR (CD_3OD): 8.45 (m, 1H), 8.40 (s, 1H), 8.34 (s, 1H), 7.62 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 8.6 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 5.04 (m, 1H), 4.0 (m, 2H), 3.9 (m, 2H)
Example 180: MS (ESI): m/e 376 $(M+1)^+$
^{1}H NMR (CD_3OD): 8.47 (d, J = 8.0 Hz, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 7.6 (m, 2H), 7.55 (t, J = 7.8 Hz, 1H), 7.48 (t, J = 8.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 4.48 (dd, J = 13.2, 2.9 Hz, 1H), 4.03 (m, 1H), 3.84 (m, 1H), 3.60 (d, J = 5.3 Hz, 2H).

TABLE 11

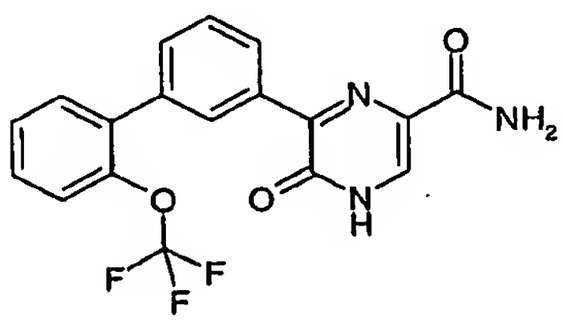


Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
181	H	OCF_3	H	H	$C(CH_3)_2CONH_2$	461
182	5-Cl	Cl	H	H	CH_2CONH_2	418
183	4- CF_3	CF_3	H	H	CH_2COOH	486
184	4- CF_3	CF_3	H	H	CH_2CONH_2	485
185	H	Cl	H	H	CH_2CONH_2	383
186	3-Cl	Cl	H	H	CH_2CONH_2	418
187	5- CF_3	CF_3	H	H	CH_2CONH_2	485
188	H	OCF_3	H	H	$CH(CH_3)COOH$	448
189	H	OCF_3	H	H	$CH(CH_3)CONH_2$	447
190	H	CF_3	H	H	$CH(CH_3)CONH_2$	431
191	H	OCF_3	H	H		460
192	H	OCF_3	H	H	$CH(CH_3)COCH_3$	446
193	H	OCF_3	H	F	CH_2CONH_2	451
194	6-F	CF_3	H	H	CH_2CONH_2	435
195	H	OCF_3	F	H	CH_2CONH_2	451
196	6-F	CF_3	H	H	$CH(CH_3)CONH_2$	449
197	H	OCF_3	F	H	$CH(CH_3)CONH_2$	465
198	4-F	OCF_3	F	H	CH_2CONH_2	469
199	4-F	OCF_3	F	H	$CH(CH_3)CONH_2$	483
200	H	CF_3	H	F	CH_2CONH_2	435
201	3-F	CF_3	H	H	CH_2CONH_2	435
202	4-Cl	CF_3	H	H	CH_2CONH_2	451
203	H	OCF_3	H	F	$CH(CH_3)CONH_2$	465

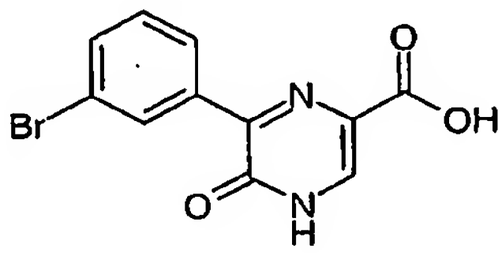
Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
204	6-F	CF_3	H	H	$CH_2CONHCH_3$	449
205	6-F	CF_3	H	H	$CH_2CON(CH_3)_2$	463
206	H	CF_3	H	H	$CH(CONH_2)_2$	460
207	H	OCF_3	H	H	$CH(CONH_2)_2$	476
208	6-F	CF_3	H	H	$CH(CONH_2)_2$	478
209	H	CF_3	H	H	$CH_2CONHCH_3$	431
210	H	CF_3	H	H	$CH_2CON(CH_3)_2$	445
211	4-CF_3	CF_3	H	F	CH_2CONH_2	503
212	H	OCF_3	H	H	$CH_2CON(CH_3)_2$	461
213	H	OCF_3	H	H	$CH_2CONHCH_3$	447
214	H	OCF_3	F	H	$CH_2CONHCH_3$	465
215	H	OCF_3	H	F	$CH_2CONHCH_3$	465
216	6-F	CF_3	H	H	$CH_2CONH(CH_2)_2OH$	479
217	H	CF_3	H	F	$CH_2CONHCH_3$	449
218	H	OCH_2CF_3	H	H	CH_2CONH_2	447
219	H	$OCH_2CF_2CF_3$	H	H	CH_2CONH_2	497
220	6-F	CF_3	H	H	CH_2CONH	475
221	H	CF_3	H	H	CH_2CONH	457
222	6-F	CF_3	H	H	$CH_2CONHCH(CH_3)_2$	477
223	6-F	CF_3	H	H	$CH_2CONHC(CH_3)_3$	491
224	H	CF_3	H	H	$CH_2CONHC(CH_3)_3$	459
225	4-F	OCF_3	H	H	CH_2CONH_2	451
226	H	CF_3	H	H	$CH_2CONHCH_2CH_3$	445
227	H	CF_3	H	F	$CH_2CONHCH_2CH_3$	463
228	6-F	CF_3	H	H	CH_2CON 	493
229	6-F	OCF_3	H	H	CH_2CONH_2	451
230	6-F	CF_3	H	H	CH_2CON 	511
231	5-F	OCF_3	H	H	CH_2CONH_2	451
232	6-F	OCF_3	H	H	CH_2COOH	452
233	H	OCF_3	H	OCH_2Ph	CH_2CONH_2	539
234	H	OCF_3	H	OCH_2Ph	$CH(CH_3)CONH_2$	553

Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
235	H	CF_3	H	H		485
236	5-I	OCF_3	H	H	CH_2CONH_2	559
237	6-F	CF_3	H	H	CH_2COCH_3	434
238	H	CF_3	H	H	CH_2COCH_3	416
239	H	CF_3	H	H		514
240	H	CF_3	I	I	CH_2CONH_2	669
241	5-F	OCF_3	H	F	CH_2CONH_2	469
242	4-F	CF_3	H	F	CH_2CONH_2	453
243	H	OCF_3	H	H	CH_2COCH_3	432
244	H	CF_3	H	H		475
245	H	OCF_3	Br	H	CH_2CONH_2	512
246	H	OCF_3	H	F	CH_2COCH_3	450
247	5-F	CF_3	H	H	CH_2COCH_3	434
248	5-F	CF_3	H	H		475
249	H	OCF_3	F	H	CH_2COCH_3	450

EXAMPLE 250



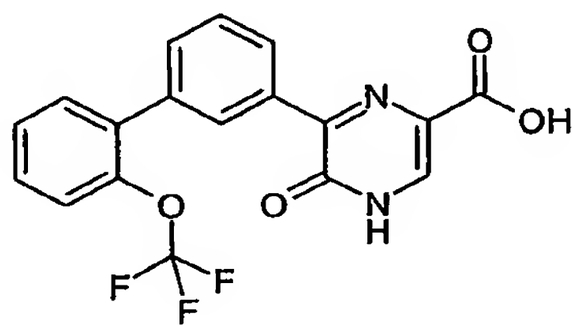
Step 1: Preparation of:



A 50-ml round-bottom flask fitted with a stirbar and septum was flushed with N_2 and charged with the keto methyl ester (from Step1 Example 1) (0.500 g), anhydrous methanol (10 mL), and methyl 2,3-diaminopropionate (0.772 g) [prepared from 2,3-diaminopropionic acid, commercially available from Sigma-Aldrich]. To the resulting mixture (a white suspension) was added sodium methoxide solution (3.4 mL, 25% w/w) dropwise over 5 min. The yellow reaction mixture, thus obtained, was stirred at room temperature under air for 30 min before being concentrated *in vacuo*. The resulting yellow solid was acidified with 1N HCl (50 mL) and extracted (2 X) with EtOAc (50 mL). The combined organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude pyrazinone carboxylic acid obtained was dried under vacuum and then purified by reversed-phase chromatography using acetonitile and water.

^{1}H NMR (d_6-DMSO): 8.49 (t, J = 1.8 H_z, 1H), 8.42 (d, J = 8.1 H_z, 1H), 8.09 (s, 1H), 7.66 (m, 1H), 7.43 (t, J = 8.0 H_z, 1H).

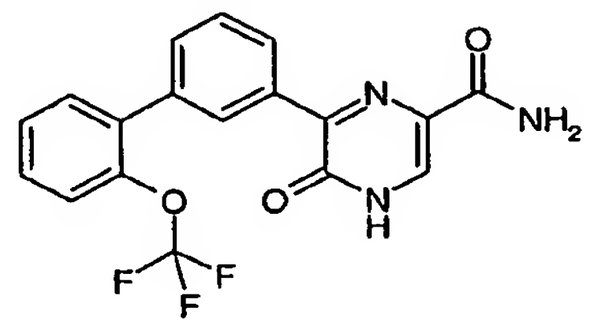
Step 2: Preparation of



To a 250 ml Schlenk flask equipped with a stirring bar was charged with of 2-trifluoromethoxyphenyl boronic acid (1.0 g) and the bromophenylpyrazinone carboxylic acid (from Step 1 above) (1.0 g), followed by EtOH (15 mL) and 1M Na_2CO_3 (20 mL). The reaction mixture was flushed with N_2 and Pd(dppf)Cl2 (69 mg) was added. The mixture was heated at 95 °C for 1 h and then at 80 °C overnight. The reaction was cooled to room temperature and volatiles were removed under reduced pressure. The residue obtained was dissolved in 2 % KOH (80 mL) and the resulting mixture was filtered through a pad of celite to remove highly colored palladium residue. The filtrate was acidified with 3N HCl and extracted with EtOAc (75 mL; 2X). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product (1.2 g). This material was further purified by recrystallization from mixed solvent of CH_3CN and H_2O to give 0.71 g pale brown solid.

^{1}H NMR (CD_3OD): 8.41 (s, 1H), 8.36 (d, J = 7.8 H_z, 1H), 8.24 (s, 1H), 7.66 (d, J = 7.3 Hz, 1H), 7.60 (t, J = 7.6 H_z, 1H), 7.52 (d, J = 6.8 Hz, 1H), 7.42 (m, 3H).
MS (ESI): m/e 377 $(M+1)^+$

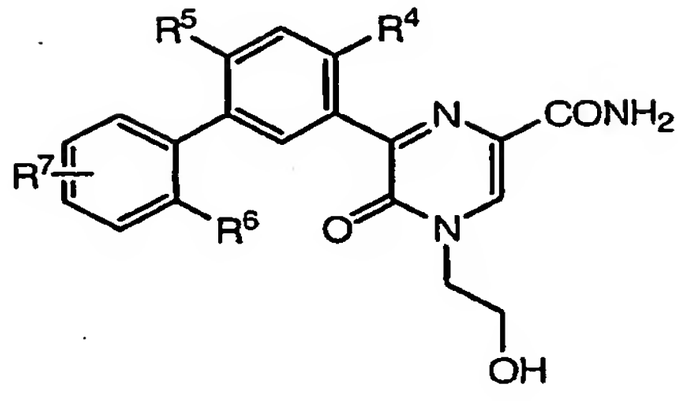
Step 3: Preparation of:



To a solution of the carboxylic acid from Step 2 (0.707 g) in anhydrous DMF (5 mL) was added CDI. The resulting reaction mixture was stirred at room temperature for 10 minutes and at 50 °C for 15 more minutes. After cooling to room temperature, NH_4OAc (1.0 g) was added as a solid. After stirring at room temperature over night, reaction mixture was diluted with water (100 mL). The precipitate formed was filtered and washed with water and air dried to yield the final amide product as pale yellow solid (0.67 g).

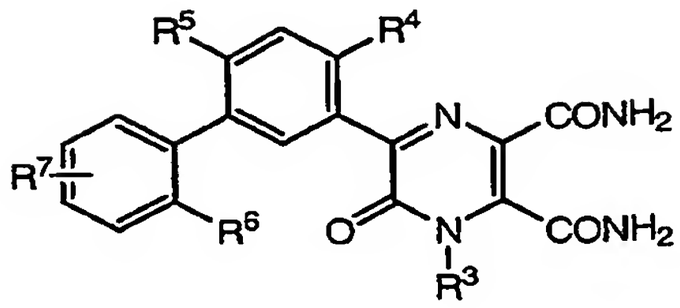
^{1}H NMR (CD_3OD): 8.51 (s, 1H), 8.42 (m, 1H), 8.08 (s, 1H), 7.6 (m, 3H), 7.48 (m, 2H), 7.43 (m, 1H).
MS (ESI): m/e 376 $(M+1)^+$

TABLE 12



Example #	R^7	R^6	R^5	R^4	(m/e) (M+H)
251	4-F	CF_3	H	H	422
252	6-F	CF_3	H	H	422
253	3-F	CF_3	H	H	422
254	H	CF_3	F	H	422
255	H	CF_3	H	F	422
256	5-CF_3	OCF_3	H	H	488
257	4- F	OCF_3	H	H	438
258	H	OCF_3	F	H	438
259	H	OCF_3	H	F	438
260	4-F	CF_3	H	F	440
261	3-F	CF_3	H	F	440
262	H	O $CH_2CF_2CF_3$	F	H	502
263	4-F	OCF_3	F	H	456
264	4-CF_3	CF_3	H	H	472
265	5-Cl	Cl	H	H	405
266	5-CF_3	CF_3	H	H	472
267	5-F	CF_3	H	H	422
268	4-F	OCF_3	H	H	438
269	5-F	OCF_3	H	H	438
270	H	OCF_3	H	OCH_2Ph	526
271	H	OCF_3	Br	H	499
272	4-Cl	CF_3	H	H	451

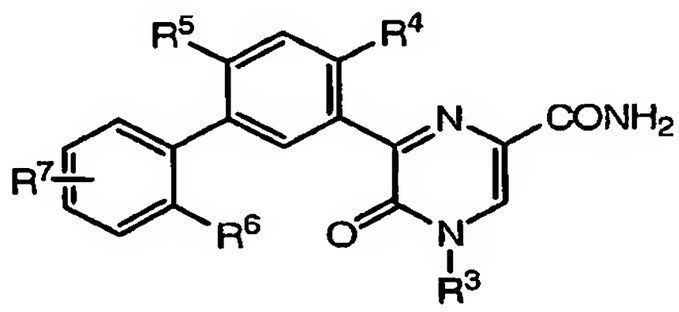
TABLE 13

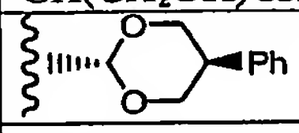


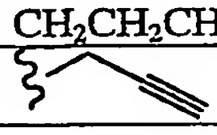
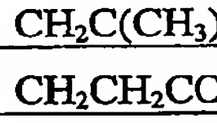
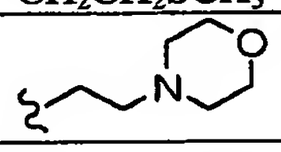
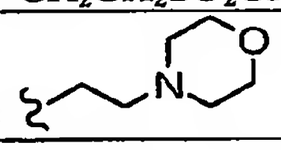
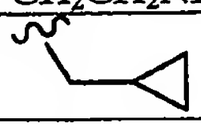
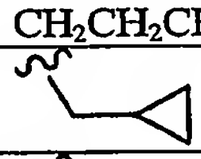
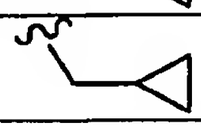
Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
273	H	OCF_3	H	H	CH_3	433
274	H	CF_3	H	H	CH_3	417
275	H	CF_3	H	H	H	403
276	H	OCF_3	H	H	H	419
277	4-F	CF_3	H	H	H	421
278	4-F	CF_3	H	H	CH_3	435
279	4-F	CF_3	H	H	CH_2CH_2OH	465
280	3-F	CF_3	H	H	H	421
281	3-F	CF_3	H	H	CH_3	435
282	3-F	CF_3	H	H	CH_2CH_2OH	465
283	4-Cl	CF_3	H	H	CH_3	451
284	5- CF_3	CF_3	H	H	CH_3	485
285	4-Cl	CF_3	H	H	H	437
286	5- CF_3	CF_3	H	H	H	471
287	4-F	OCF_3	H	H	H	437
288	4-F	OCF_3	H	H	CH_3	451
289	4-F	OCF_3	H	H	CH_2CH_2OH	481
290	4-Cl	CF_3	H	H	CH_2CH_2OH	481
291	5- CF_3	CF_3	H	H	CH_2CH_2OH	515
292	H	$OCH_2CF_2CF_3$	H	H	H	483
293	H	$OCH_2CF_2CF_3$	H	H	CH_3	497
294	H	$OCH_2CF_2CF_3$	H	H	CH_2CH_2OH	527
295	H	OCH_2CF_3	H	H	H	433
296	H	OCF_3	F	H	H	437

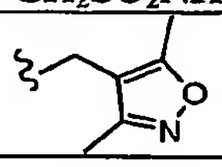
Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
297	H	CF_3	F	H	H	421
298	H	OCH_2CF_3	H	H	CH_3	447
299	H	OCF_3	F	H	CH_3	451
300	H	CF_3	F	H	CH_3	435
301	H	OCF_3	F	H	CH_2CH_2OH	481
302	H	CF_3	F	H	$CH_2CH=CH_2$	461
303	H	OCF_3	F	H	$CH_2CH=CH_2$	477
304	H	CF_3	F	H	$CH_2CH=CH_2$	465
305	H	CF_3	F	H	$CH_2CH_2OCH_3$	479

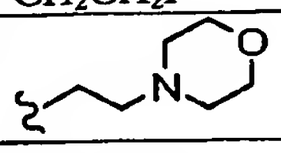
TABLE 14



Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
306	H	OCF_3	H	H	$CH_2CH_2OCH_3$	434
307	6-F	CF_3	H	H	$CH_2CH_2OCH_3$	436
308	6-F	CF_3	H	H	$CH_2CH_2OCH_2CH_3$	450
309	H	OCF_3	H	H	$CH_2CH_2CH_3$	418
310	H	OCF_3	H	H	$CH(CH_2OH)CH_2OH$	450
311	H	CF_3	H	H	$CH(CH_2OH)CH_2OH$	434
312	H	OCF_3	H	H		538
313	6-F	OCF_3	H	H	$CH(CH_2OH)CH_2OH$	468
314	H	CF_3	H	F	$CH(CH_2OH)CH_2OH$	452
315	H	CF_3	H	F	$CH_2CH(OH)CH_2OH$	452

Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
316	H	OCF_3	H	H	$CH_2CH_2CH_2CH_3$	432
317	H	CF_3	H	H	$CH_2CH(OH)CH_3$	418
318	6-F	CF_3	H	H	$CH_2CH(OH)CH_3$	436
319	6-F	OCF_3	H	H	$CH_2CH(OH)CH_2OH$	468
320	H	OCF_3	H	H		414
321	H	OCF_3	H	H	$CH_2CH_2CH_2CH_2CH_3$	446
322	6-F	CF_3	H	H		416
323	H	OCF_3	H	H	$CH_2C(CH_3)_2CH_2OH$	462
324	H	OCF_3	H	H	$CH_2CH_2CONH_2$	416
325	H	OCF_3	H	H	$CH_2CH_2SCH_3$	450
326	6-F	CF_3	H	H	$CH_2CH_2SCH_3$	452
327	H	OCF_3	H	H		489
328	H	OCF_3	H	H	$CH_2CH_2SO_2CH_3$	482
329	6-F	CF_3	H	H	$CH_2CH_2SO_2CH_3$	484
330	6-F	CF_3	H	H		491
331	6-F	CF_3	H	H	$CH_2CH_2CH_2OH$	436
332	6-F	CF_3	H	H	CH_2SCH_3	438
333	6-F	CF_3	H	H	$CH_2CH_2CH_2SCH_3$	498
334	6-F	CF_3	H	H	$CH_2CH_2CH_2SO_2CH_3$	530
335	H	OCF_3	H	H	$CH_2CH_2NHCONH_2$	462
336	6-F	CF_3	H	H		432
337	H	OCF_3	H	H	CH_2CF_3	458
338	H	OCF_3	H	H	$CH_2CF_2CF_3$	508
339	H	CF_3	H	H	$CH_2CH_2CH_2OH$	418
340	H	CF_3	H	H		414
341	H	OCF_3	H	H		430
342	H	CF_3	H	H	CH_2SCH_3	420

Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
343	H	OCF_3	H	H	CH_2SCH_3	436
344	H	OCF_3	H	H	$CH_2SO_2CH_3$	468
345	6-F	CF_3	H	H	$CH_2SO_2CH_3$	470
346	6-F	CF_3	H	H	CH_2CH_3	406
347	6-F	CF_3	H	H	$CH_2CH_2CH_3$	420
348	H	OCF_3	H	H	$CH_2SO_2NHC(CH_3)_3$	525
349	H	OCF_3	H	H	$CH_2SO_2NH_2$	469
350	H	OCF_3	H	H		485
351	4-F	CF_3	H	H	$CH_2SO_2NH_2$	471
352	H	CF_3	H	H	$CH_2SO_2NH_2$	452
353	4-F	OCF_3	H	H	$CH_2SO_2NH_2$	452
354	6-F	CF_3	H	H	$CH_2SO_2NH_2$	436
355	H	CF_3	H	H	$CH_2SO_2CH_3$	452
356	H	OCF_3	F	H	$CH_2SO_2CH_3$	486
357	4-F	CF_3	H	H	CH_2CH_3	422
358	4-F	OCF_3	H	H	$CH_2CH_2CH_2OH$	470
359	4-Cl	CF_3	H	H	$CH_2SO_2NH_2$	487
360	3-F	CF_3	H	H	$CH_2SO_2NH_2$	471
361	4-F	CF_3	H	H	$CH_2SO_2NHCH_3$	485
362	H	CF_3	H	F	$CH_2CH_2CH_2OH$	454
363	H	OCF_3	F	H	CH_2CH_2F	436
364	H	OCF_3	H	F	CH_2CH_2F	436
365	4-F	OCF_3	F	H	CH_2CH_2F	455
365	6-F	CF_3	H	H	CH_2CH_2F	424
366	H	CF_3	H	F	CH_2CH_2F	424
367	4- CF_3	CF_3	H	H	$CH_2SO_2NH_2$	521
367	H	OCF_3	H	F	$CH_2SO_2NH_2$	487
368	H	CF_3	H	F	$CH_2SO_2NH_2$	471
369	H	OCF_3	H	F	$CH_2SO_2NHCH_3$	501
370	H	CF_3	H	F	$CH_2SO_2NHCH_3$	485

Example #	R^7	R^6	R^5	R^4	R^3	(m/e) (M+H)
371	H	CF_3	H	H	CH_2CH_2F	405
372	H	OCF_3	H	H	CH_2CH_2F	421
373	3-F	CF_3	H	H	CH_2CH_2F	424
374	4-Cl	CF_3	H	H	CH_2CH_2F	440
375	5-CF_3	CF_3	H	H	CH_2CH_2F	474
376	H	OCF_3	F	H		507
377	H	OCF_3	H	F	CH_2CH_2F	437
378	H	OCF_3	F	H	CH_2CH_2F	437
379	5-F	CF_3	H	H	CH_2CH_3	406
380	5-F	CF_3	H	H	CH_2CH_2F	424
381	H	CF_3	H	H	$CH(CONH_2)_2$	460
382	H	OCF_3	H	H	$CH(CONH_2)_2$	476
383	6-F	CF_3	H	H	$CH(CONH_2)_2$	479
384	6-F	CF_3	H	H	$CH_2CONHCH_2CH_2OH$	480